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TOXICOLOGY PROGRAM
Technology Branch
Communicable Disease Center
Atlanta 22, Ga.

Monitoring of Low-Frequency Phenomena

Many physical phenomena occur at frequencies which are generally so low that they require visual attention during monitoring or recording. Whether such phenomena are detected through their concomitant electric activity [for example, electric activity of the heart (ECG) or brain (EEG)] or through the use of electric transducers (for example, for measuring blood pressure or other fluctuating pressures), audio monitoring frees the visual attention of the experimenter for the observation of other phenomena or for the performance of other tasks. The experimenter is given a constant indication of the experiment and may be confident that he will hear any changes as soon as they happen.

A transistor regenerative oscillator was adapted from an experimental model (*1*) to convert subaudible frequencies into audio frequencies. Other transistor oscillators have been described (*2*) which could be similarly adapted. The frequency of oscillation of the oscillator varies inversely with the supply voltage. Furthermore, the power requirements are so low (a 50-μw input gives a 400-cy/sec tone) that the oscillator may be powered directly by the electric signal. Thus, amplitude variations of an otherwise inaudible signal, whether they are periodic or random in nature or even slow changes in a steady level, are translated into tonal variations. The audio-frequency tones produced may be, with experience, of great diagnostic or interpretive value. However, the device was designed as a monitor, since visual patterns are usually easier to study and interpret.

The monitor was designed to be connected across the coils of a recording galvanometer (for example, an electroencephalograph or electrocardiograph) but can be used with any other source providing more than 0.5-v input to the monitor. The output can be fed into a loudspeaker system or high-impedance earphones. The device is simple, self-contained, reliable, and inexpensive (about $10 for parts). More elaborate, but less versatile, heart monitors have been available commercially (*3*).

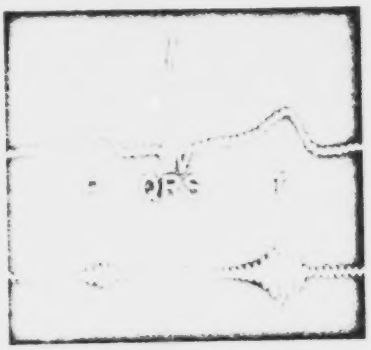

Fig. 2. Oscilloscope tracing of normal human electrocardiogram (top) with output from the audio monitor (bottom). The P wave gave a high-frequency tone followed by the QRS complex, which gave a short, low-pitched tone. The T wave gave a softer, medium-pitched, prolonged tone.

The basic oscillator gives an 1800-cy/ sec tone at 0.2-v input, a 200 cy/sec tone at 0.75-v input, and a 50-cy/sec tone at 2-v input. Below about 400-cy/sec, the tone is more in the nature of a pulse than the sine wave found at higher frequencies. The load on transformer T2 (Fig. 1) affects the quality of the tone. Polarity is important. If no oscillations are produced when about 1.0 v is applied to the basic oscillator, the leads of the secondary of transformer T1 should be reversed. The diodes and transistor are damaged by heat, so the leads should be kept long, and a hemostat or pair of pliers should be used as a heat sink when soldering.

Several refinements were added. (i) A sensitivity control, R1, regulates the input voltage required for a given tone. At maximum sensitivity, 0.5 v gives an 1800-cy/sec tone, whereas 5 v are needed at mid-range, and more than 100 v at nearly zero sensitivity. (ii) A clipping circuit consisting of a 1.4-v mercury battery and a crystal diode, CR1, was added to give the device a roughly logarithmic response. This prevents the suppression of low-level components in a signal with a wide dynamic range. As an example, the QRS component of the electrocardiograph (Fig. 2) has a much higher amplitude than the P and T waves, and thus tends to overpower their tone. The T wave, however, is of particular interest because changes in amplitude or polarity indicate anoxia or heart damage. When the series resistances from R1 plus R2 and from R3 are both greater than 20,000 ohms, the signal going to the oscillator is sharply limited to about 1.4 v. (iii) Variable resistor R3 acts as a tone control for the clipped segments, such as the QRS. Thus, 1.4 v coming from the "clipper" can be set to give a tone from 300 to 2000 cy/sec. (iv) The bias network, R4 through R7 and B2, acts to suppress noise or the effects of power-amplifier imbalance by adding a negative voltage which the signal must overcome to energize the oscillator. By setting it to give a positive voltage, a steady baseline tone is produced which may then be frequency modulated by the signal. A switch is needed on B2 because of the low resistance load, whereas diode CR1 acts as an effective switch for B1. (v) The diode, CR2, rectifies the signal since the oscillator operates only with the polarity indicated (and may be damaged by currents of opposite polarity). For instance, an inverted T wave of an electrocardiogram causes a lack of tone when the bias control is set in the neutral position. A polarity reversing switch in the input circuit is a helpful addition. (vi) The transformer T2 is used to increase the amplitude of oscillator output signal and also to isolate the monitor from the speaker system, since the galvanometers of many direct-writing oscillographs are not at ground potential. Figure 2 shows how this device treats a complex input waveform by converting it to bursts of audio frequencies of different tones and amplitudes.

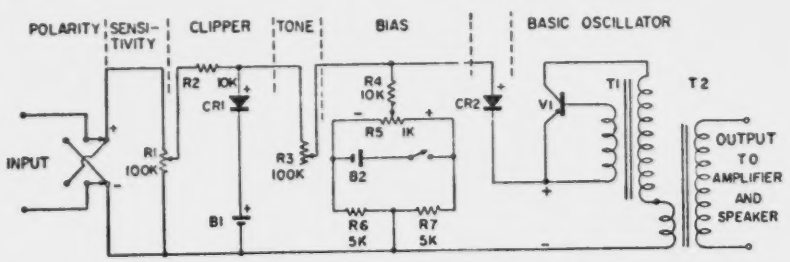

Fig. 1. Schematic diagram of frequency-modulated oscillator: K, 1000 ohms; CR1 and CR2, 1N56 high-conduction germanium diodes; V1, CK 722 p-n-p junction transistor; T1, 1/3 interstage transformer; T2, microphone transformer; B1 and B2, 1.4-v battery.

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PESTICIDE
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Information on Health Aspects of Pesticides*

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Since DDT, first of the modern synthetic pesticides, was introduced commercially in 1945, the amount of pesticide chemicals used in the United States has increased tremendously. This is reflected currently by the Federal registration of more than 60,000 formulations, each containing one or more of some 800 different pesticidal compounds.[1] The literature of pesticides increased proportionately, an increase which closely parallels the general growth pattern of all scientific literature. At the 1963 meeting of the American Chemical Society, a panel of four distinguished scientists met to evaluate the pesticide information problems, and among the problems defined were the following:[2]

1. The need for rapid and complete retrieval of pesticide information by government agencies.
2. The difficulty of maintaining awareness to the degree necessary for keeping the teaching of pesticides as current as possible.

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* Presented before the Division of Chemical Literature, Symposium on Toxicological Information Centers, 156th Meeting, ACS, Atlantic City, N. J., September 9, 1968.

3. The difficulty of doing pesticide-oriented literature searches on classes of compounds indexed in the conventional manner.

The Pesticides Program of the Public Health Service has been studying the possible effects of pesticides on human health for a number of years and has been collecting literature on the toxicology of pesticides since 1950. This collection at the present time consists of approximately 17,000 references and is continuously growing by regular scanning of the published literature. Although there are no figures available to show the year-to-year increase in the size of the collection, it is estimated that the collection grew about four times faster from 1961 to the present time than it did from 1950 to 1961.

DESCRIPTION OF THE PRESENT SYSTEM

The existing system is a manual system consisting of recording pertinent references on standard 5 inch × 3 inch library cards, which are filed by author and subject. Hard copy is available for approximately 25% of the references. For the other 75% of the references, original articles are not in the collection either because they can be found in the library of the National Communicable Disease Center or because they were not readily available.

The classification system is similar to the Dewey Decimal System except that two decimal sequences are used, one to express the main heading and the other a subheading. The references are classified by main heading, such as Chemistry, Physics, Biology, and within each main heading into several subheadings. A heading is represented by a sequence of numbers set off by distinct punctuation. Each heading is further subdivided in hierarchical fashion. These headings are printed on the upper left portion of the card one below the other as shown in Figure 1. The authors, title, and other bibliographic elements are printed below. Incidentally, the initial letter "S" in the main heading is identical in meaning to the figure "10;" both indicate substance. To avoid useless duplication, only certain headings (designated by letters) may be used as main headings. Thus, the sequence *toxicity of endrin* is changed and only the sequence *endrin toxicity* is permitted.

Subject and author cards are produced from the same stencil but are distinguished by color. Subject cards are filed numerically and author cards alphabetically. In addition to the collection in the Pesticides Program in Atlanta, duplicate copies of all reference cards are maintained at the Western Pesticides Laboratory, Wenatchee, Wash., and the Pesticides Research Laboratory, Perrine, Fla.

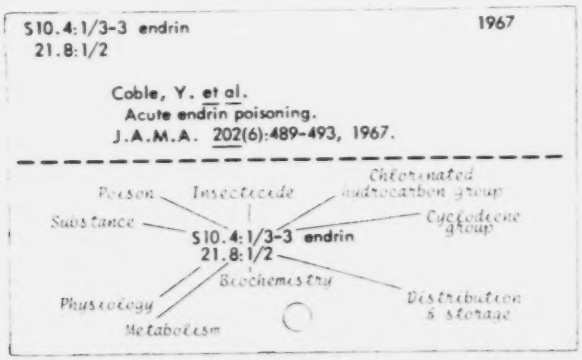

Figure 1. A typical index card. The portion below the broken line is not a part of the card but has been added to explain the subject classification

INVESTIGATIONS RELATED TO A PESTICIDES INFORMATION SYSTEM

Approximately two years ago, a contract was let by the Pesticides Program to perform a preliminary study of the informational requirements of the users of a health oriented Pesticides Information Center. The work under this contract included the compilation of a thesaurus covering the health and medical aspects of pesticides, a limited system of Selective Dissemination of Information (SDI), and publication of an abstract bulletin on an experimental basis.

The potential users interviewed for the SDI system were all government personnel or persons working under contract to the government. The purpose of the interviews was to define the users' needs for information, their habits in obtaining information, their vocabulary, their educational background, and their professional activities. The SDI system was of the usual type in which the index terms of the documents were matched against the users' interest profiles. When matches occurred, the pertinent abstracts printed on 8 inch × 5 inch cards were sent to the users along with a questionnaire designed to evaluate the usefulness of the references to the users. One tentative conclusion that emerged from this evaluation was that SDI is not universally applicable or desirable in all research situations, particularly in relatively narrow fields in which specialized abstracting and indexing publications are available. It was found that persons working on the periphery of the field favored an SDI system, whereas, scientists working on the toxicology of pesticides preferred to do their own searching.

The contractor also prepared an abstract bulletin on the health aspects of pesticides on an experimental basis. Each issue of the abstract bulletin contained about 150 abstracts of papers published in about 500 different journals. Copies of each issue were mailed to about 200 selected persons who were actively engaged in the pesticides field. The users' response indicated that this abstract bulletin was very useful to them as a current awareness tool in the field.

ABSTRACT BULLETIN ON THE HEALTH ASPECTS OF PESTICIDES

Since the response to the experimental abstract bulletin indicated that there was a need for this type of abstract service, it was decided to resume the regular publication of an abstract bulletin. A contract was let in June 1968, to prepare this abstract bulletin on a regular basis, and the first issue is scheduled to appear the latter part of 1968. Under this contract, the contractor scans regularly approximately 500 journals in which the majority of articles on the health aspects of pesticides are usually published as well as other publications including reports and proceedings of meetings. The title of the abstract bulletin, which will be published monthly, will be *Health Aspects of Pesticides*, and will be available from the Government Printing Office at an annual subscription price of $2.75.

Table I. Divisions of the *Health Aspects of Pesticides* Abstract Bulletin

1. General	4. Toxicology and Pharmacology
2. Monitoring	5. Safety
3. Epidemiology and Treatment	6. Analysis

The abstracts in the bulletin will be of the informative type as far as possible, and abstracts of foreign publications will also be included. The abstracts will be grouped into six categories as shown in Table I. The abstracts in the bulletin will follow closely the format and rules established by *Chemical Abstracts*. There will be annual author and subject indexes for the convenience of the user.

Other services to be performed under this contract include expansion of the thesaurus which was developed under the previous contract and a computerized system by which it will be possible to retrieve information automatically. It is anticipated that the mechanized retrieval will not be very useful until several thousand abstracts accumulate making manual searching time-consuming and ineffective. The primary purpose of the abstract bulletin for the immediate future is, of course, current awareness rather than retrospective searching.

FUTURE PLANS FOR PESTICIDES INFORMATION SYSTEM

The current collection of about 17,000 references on the toxicology of pesticides will be strengthened by the references that will result from the publication of the abstract bulletin. Reference cards for the papers in the abstract bulletin will be prepared and added to the central collection in Atlanta as well as to the satellite collections in the various laboratories of the Pesticides Program. In the future, abstract cards will be produced from the magnetic tapes used in the production of the abstract bulletin, and it will be possible to expand their distribution to selected laboratories which are involved in the toxicology of pesticides. The cards will continue to be coded according to the system used in the Pesticides Program, and those laboratories receiving copies of the cards will also receive detailed instructions on the system of classification. In addition, the new cards will carry keywords, so the laboratory receiving them will have a choice of the classification system they use. The advantage of the system used by the Pesticides Program is economy. Classification is assigned by an experienced person and printed directly on the card, which may be filed by a clerk. The use of keywords for indexing—for example, by use of a peek-a-boo system—would offer the advantage of flexibility and somewhat greater depth of indexing; however, its maintenance in each laboratory using it would require considerable time of professionally trained personnel. As the information system is developed over the years, a sizable collection of references will be stored on the computer tapes. Eventually, in several years' time, it will be possible to search these tapes for specific references to particular subjects. It is hoped that this retrospective searching of the files can be made available as a service to those working on the toxicology of pesticides.

This information system is designed to provide a broad informational background for all persons working in the field of the health aspects of pesticides. In the abstract bulletin there is no attempt to go beyond the area of pesticides. Naturally, professional chemists working in this field will require references concerned with other aspects of chemistry, but it is hoped that the abstract bulletin will be a start on which they can build their own specific information systems.

One of the roles of the Pesticides Program is to provide assistance to state and local health departments in building and strengthening their own competence in the problems related to pesticides and public health. It is believed that the abstract bulletin, *Health Aspects of Pesticides*, and the related services of the information system will be of great assistance to these departments of health.

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INDUSTRIAL MEDICINE AND SURGERY, 37(7):519, July 1968.

Some Health Related Needs in Pesticide Investigations

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270

PESTICIDES PROGRAM
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Pesticides have become inescapable elements of our environment and it is important that we use them safely. Methods for screening pesticides for hazard to man must be improved. The problem of potentiation and antagonism in the simultaneous exposure to certain pesticides and drugs and between different pesticides should be investigated further. A study is needed of storage of the organochlorines by the fetus *in utero* and possible effects. Improvement of analytical techniques and a certain degree of standardization of procedures is needed so that data can be more meaningful. Other major areas of concern are the relative lack of epidemiological investigations of chemical poisonings, the need for surveillance of occupationally exposed persons, routine monitoring of man and the environment, and the lack of reporting of poisoning cases. Additional needs include development of improved diagnostic procedures for poisoning and studies on mode of action of pesticides. State training programs for chemists and epidemiologists are needed, and information on the safe use of pesticides should be made available to the public. Problems associated with disposal of pesticide wastes and containers and transportation and storage of pesticides, particularly with edible materials, are urgent. There is a need for more uniformity in State regulations governing pesticides. The biological magnification of pesticides in their passage through the food chain needs to be better understood. Non-chemical means of pest control based on microorganism or toxins derived from them require the same intense investigation for health hazards as synthetic pesticides.

Los pesticidas son elementos presentes en nuestro medio ambiente y es importante manipularlos con medidas de seguridad. Métodos para determinar el riesgo que los mismos representan para el hombre deben ser mejorados. La exposicifln simultánea a distintos pesticidas implica problemas de aumento de potencia y antagonismo. Es necesario conocer el almacenamiento de los insecticidas cuando el feto aún se encuentra in utero. Es necesario mejorar los métodos analíticos. Otras áreas que requieren estudios son la epidemiología, vigilancia de las personas expuestas en su trabajo, determinación de la concentración en el medio ambiente y que las autoridades sean informadas de los casos de intoxicaciones. También es necesario desarrollar métodos diagnósticos, así como modo de acción de los pesticidas. Es necesario que los estudios desarrollen programas de entrenamiento para químicos y epidemiologos, y hacer conocer al público cómo manipular estos agentes. Se sugiere uniformidad en las regulaciones estatales.

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THE BIOLOGICAL IMPACT OF PESTICIDES IN THE ENVIRONMENT

Proceedings of the Symposium

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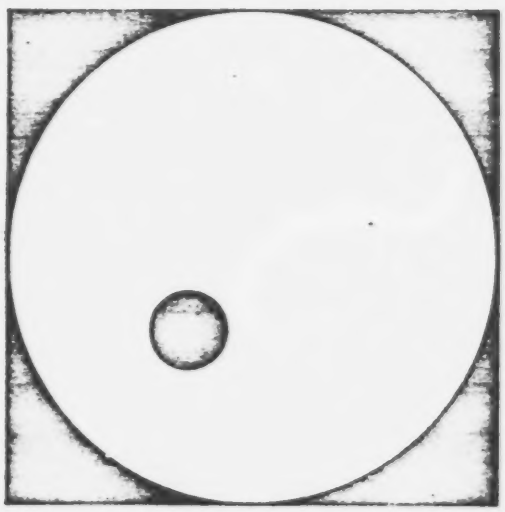
James W. Gillett, Editor



Environmental Health Sciences Series No. 1

BENEFITS OF PESTICIDES IN PUBLIC HEALTH PROGRAMS

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Pesticidal chemicals provide primary control mechanisms for insect vectors of a number of diseases of significant public health importance. The present paper will review some of the accomplishments toward control of these diseases through use of the modern synthetic pesticides. A balanced public health view of pesticide usage must also include evaluation of potential toxic side effects on human health. This problem will also be reviewed.

The effectiveness of the modern pesticides against a wide range of disease vectors has made possible the control of many important diseases which previously defied all practical efforts at control. DDT has contributed to the control of at least 27 diseases (Simmons, 1959). Among the diseases whose vectors appear to be susceptible to control by pesticides are malaria, filariasis, dengue, urban yellow fever, virus encephalitis, louse-borne typhus, louse-borne relapsing fever, trench fever, plague, murine typhus, dysentery and diarrhea, leishmaniasis, bartonellosis, onchocerciasis, sandfly fever, trypanosomiasis, yaws, infectious conjunctivitis, cholera, chagas' disease, scrub typhus (tsutsugamushi), scabies, rickettsial pox, tick-borne diseases, and tularemia. As early as 1953, it was estimated that at least 5 million lives had been saved and 100 million illnesses prevented through the use of DDT for controlling malaria, typhus, dysentery, and other arthropod-borne diseases (Knipling, 1953).

Control of malaria represents most dramatically the results of disease control through use of pesticides. Malaria was at one time a very important disease in parts of the United States. For example, there were 112 deaths and several thousand cases of malaria in California in 1910 (Barnes, 1953). Intensive control measures against the mosquito gradually reduced the disease, but it was not until DDT became available that malaria was virtually eradicated from this country. Statistics from many other countries are even more impressive. The number of cases of malaria in Greece was reduced from a million in 1938 to 1200 in 1958 through an aggressive control campaign based on use of DDT (Simmons, 1959).

Protection of personnel exposed to hazards of disease vectors and pests is a major problem for the military as well as to civilian hunters, campers, and others. Repellents are now available which provide protection from biting pests and minimize the possibility of contracting arthropod-borne diseases.

Finally, control of certain species of pest insects, such as houseflies, cockroaches, and various innocuous mosquito species, contributes, if not specifically to public health, at least to a sense of well-being. Pesticides also provide through the use of modern herbicides the potential for control of allergy-producing weeds such as ragweed and poison ivy on farms, in cities, recreational sites, and other areas.

In considering public health benefits of pesticides, attention should be called to the role of these chemicals in bringing about increased production of food as discussed by Mr. Walker in the preceding paper in this symposium. The need for increased food production to feed the expanding population is evident from the fact that malnutrition and starvation are among the most urgent world public health problems.

Chemicals provide an effective and practical way to control insect- and rodent-borne vectors of human disease. However, the necessity of using these toxic chemicals on man or on his immediate environment has created potential hazards that are of great public health significance.

Analysis of statistics on mortality in the United States from accidental poisoning indicates that pesticides are responsible for about 150 deaths per year or about 10 percent of the deaths from all solid and liquid poisons. The annual death rate associated with all pesticides in the United States is 1.0 per million population (Hayes, 1964).

Almost all of these deaths are due to accidental ingestion, suicide, homocide, or occupational poisoning of workers. The majority of the deaths caused by pesticides has involved children who found and ingested one of the compounds. The children obtain the material from bottles or packages left within their reach. Unlabelled containers, especially soft drink bottles, constitute a particular hazard. Many children have been killed by poison remaining in packages that have been discarded as empty.

Statistics on morbidity due to pesticides are much less precise. According to the best estimate available, the ratio of non-fatal to fatal cases of poisoning is about 100 to 1 (Hayes, 1969). In California, reports of occupational poisoning by pesticides is required under the California Workmen's Compensation Law (West and Milby, 1965). Between 1960 and 1963, the annual number of reports of work injury from pesticides in California has ranged from 827 to 1013.

Foremost among the pesticide compounds which have caused public concern because of their persistence is DDT. DDT and its congeners are stored in body fat in exposed animals. The earliest published report of DDT storage in man is apparently that of Howell (1948). He found DDT-derived material at a concentration of about 7 ppm in the fat of a man with occupational exposure for 4 yrs and a history of eating foods known to bear appreciable residues. The first general survey for DDT was carried out by Laug and his colleagues in 1950 (Laug et al., 1951). They demonstrated DDT residues ranging from 0 to 34 ppm (mean, 5.3 ppm) in the fat of 75 persons with no special occupational exposure.

Since the 1950 study by Dr. Laug and his

co-workers, a number of surveys have been conducted in various areas of the country to define the DDT storage level more exactly and to study its changes with time and geographic location. The results show that DDT is found in practically everyone in the general population of this country. The present mean storage level is about 3 ppm for DDT and about 8 ppm for metabolites of this compound, giving a total of 11 ppm of DDT-derived material (Durham, 1969). However, there has been no significant increase in the storage of DDT by the general population of the United States since it was first measured in 1950. Studies in volunteers have shown that the excretion of DDT is very slow in man (Hayes et al., manuscript in preparation). Thus, any decrease in storage of DDT as the result of decrease of DDT levels in food or other environmental media would be only slowly reflected in decreased fat storage levels of the compound.

Other chlorinated hydrocarbon pesticides in addition to those derived from DDT which are stored at detectible levels in body fat of the general population of this country include the gamma isomer of hexachlorocyclohexane, dieldrin, and heptachlor epoxide, all of which are present at mean levels below 1 ppm. The sensitive technique of electron capture gas chromatography has also made possible measurement of these compounds at the very low levels at which they occur in blood.

The concern is, of course, whether or not DDT storage levels of this magnitude are harmful to man. In this regard studies of men with prolonged occupational exposure are of particular interest. In 2 such studies, Ortelee (1958) and Laws et al. (1967) conducted clinical examinations and laboratory tests, including determination of DDT storage and DDA excretion, on groups of 40 and 35 men, respectively, with intensive and prolonged occupational exposure to DDT. Fat storage levels of DDT-derived materials ranged up to 647 ppm. These men showed no ill effects as judged by medical examination, their own reports, or their work attendance records.

Stein and Hayes (1964) surveyed 1100 pest control operators, most of whom had lengthy exposure to pesticides, regarding their health status. Their sick leave use was low, averaging 3 days per year. Cases of acute toxicity, dermatitis, and 2 cases of hay fever were related to exposure to pesticides. Aside from these reports, which were not frequent and were serious in only a few instances, the health of pest control personnel and of their families did not seem to be influenced to any significant degree by pesticides.

More extensive studies on exposed workers are now underway in contract studies being carried out by the Division of Community Studies, FDA. There are 15 of these Community Studies projects in areas of heavy pesticide usage throughout the United States. As one part of their contract, each project is asked to compile pesticide exposure and medical records of about 100 selected, high-exposure individuals. A group of individuals with minimal pesticide exposure serves as control. There are 8 of these Community Study projects in the Western states. They are located in Washington, California, Arizona, Idaho, Utah, Colorado, Iowa, and Texas.

Pesticides have been responsible for several episodes of mass poisoning, sometimes causing near hysteria in the local community affected. Most of these incidents have involved contamination of food with pesticides during transport. The earliest reported incident of this sort occurred in Britain in 1956 where 49 people became ill after eating bread made from endrin-contaminated flour (Davies and Lewis, 1956). This flour became contaminated during shipment in a railway car in which endrin had previously been spilled. There were no fatalities in this group of cases. Over 100 deaths in India during the Spring of 1958 resulted from eating grain accidentally contaminated with parathion during shipment (Karunakaran, 1958). In Singapore in 1959, in an outbreak of parathion poisoning due to contaminated barley, 35 children and 3 adults became ill and 9 children died (Kanagaratnam et al., 1960). In this episode, quick, decisive action by public health authorities was responsible for holding injuries to a minimum. An announcement was made by the Ministry of Health only 16 hrs after the first case was admitted to a hospital. Radio programs were interrupted every 15 min to broadcast a warning and vans equipped with loudspeakers toured the streets spreading the news. There have been no reported incidents in the United States involving mass illness from food contaminated with pesticide during shipment. However, several children were made ill by wearing clothing which was unknowingly contaminated with mevinphos during shipment (Warren et al., 1963). A mass incident of poisoning from parathion-contaminated flour and sugar involving 16 deaths and many illnesses occurred just across our southern border in Tia Juana, Mexico (Marquez-Mayaudon et al., 1968).

The toxicity of known oral doses of DDT has also been studied in volunteers (Hayes et al., 1956; Hayes et al., manuscript in preparation). A total of 90 men were involved in the study. The subjects were divided into 3 groups, which received DDD dissolved in corn oil at doses of 0, 3.5, and 35 mg per man per day for periods up to 2 yrs. These latter doses were chosen as being about 20 and 200 times, respectively, the ordinary dietary level of DDT. The highest dose chosen was about one-fifth of that estimated to cause transient mild sickness, based on animal experiments and on the smallest single acute dose known to produce mild illness in man. No clinical effect associated with DDT dosage was detected by the men themselves or by careful physical examination and laboratory testing. The storage of DDT in body fat was found to be proportional to the dose. About 1 year was required for the men to reach equilibrium of DDT storage. Following this time no increase in DDT storage level occurred, although the men remained on the dose for an additional 1-yr period. The loss of DDT from body fat storage was found to be quite slow, however.

Reliable figures are apparently not available for the fraction of total pesticide production in this country which is used in public health vector control programs. However, it would appear that the amount is relatively

small in relation to that used in agriculture. At least for dieldrin and DDT, there is evidence that the major part of the exposure of the general population of the United States can be accounted for by residues on food. This evidence is based on the relationship between dosage and storage of these compounds in man (Durham, 1969). Thus, on the intake/storage curves for both DDT and dieldrin, the closeness of fit of the points for the general population, for which dosage aspects were determined solely by dietary intake of the pesticide, would seem to indicate that this source accounts for the greater part of the exposure to these compounds of the general population in this country. This result confirms the conclusion reached independently by Campbell and his colleagues (1965) that food contributes over 90 percent of the DDT absorbed by people in the general population.

However, Radomski and Deichmann (1969) concluded that the home usage of pesticides was one, if not the major, factor in the occurrence of elevated storage levels of DDT and DDE.

The public health significance of pesticide-induced microsomal enzyme activity must be evaluated. The harmful effect of this enzyme induction in relation to reduced egg-shell thickness in birds had been discussed earlier in this symposium by Dr. Stickel. Similar steroid-related effects have apparently not been reported in man, although increased steroid metabolism has been noted in association with enzyme stimulation in rats. However, it has been noted that, in some instances, enzyme induction produced by concomitant drug therapy has caused tolerance to a desired therapeutic effect of an administered drug. For example, phenobarbital administration significantly increased the required maintenance dosage of bis-hydroxycoumarin by patients receiving long-term anticoagulant therapy (Goss and Dickhaus, 1965).

The microsomal enzyme inductive effect of DDT has been utilized therapeutically by Thompson et al. (1969) who treated a case of familial unconjugated non-hemolytic jaundice with DDT. The patient was given 90 mg. of DDT per day orally for 6 mo. His plasma bilirubin fell to the normal range soon after treatment was begun and remained normal during 7 mo. after cessation of DDT dosage. No side-effects were noted.

On the other hand, drugs may also influence pesticide metabolism. Davies et al. (1969) have reported lowered blood levels of DDE in patients taking the anticonvulsant drugs phenobarbital and diphenylhydantoin.

In summary, the data now available indicate that as long as pesticide residues remain at the present levels they are not considered hazardous to human health. However, continued surveillance and research into biological effects are necessary to assure that subtle effects from continued low level exposure do not occur and also to detect possible harmful effects of new compounds.

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PESTICIDES PROGRAM
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EFFECT OF PESTICIDES ON HUMAN HEALTH

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Mortality from Pesticides in the United States

In the United States, the death rates associated with accidental poisoning by gases and vapors and by solids and liquids have remained relatively stable since 1939, when the present method of counting was established. There was no significant change in the rate of poisoning when DDT was introduced experimentally in 1942 and commercially in 1946, nor from the introduction of a wide variety of other new pesticides beginning about 1946. The rate for all accidental poisoning in this country for the last 25 years has been about 2 per 100,000 population, a rate only about half that for comparable poisoning reported between 1900 and 1910. The foregoing statements are based on official figures from the National Office of Vital Statistics. As with much of what follows, I have discussed the statistics in detail in a report published in 1960 (8).

In different years, deaths from pesticides have accounted for 7.8% to 12.8% or an average of about 10%, of deaths from all solid and liquid substances. The percentage is not increasing, but, in cities, the proportion tends to be lower -- 4.3% in one study. Fumigants contribute only a very small and relatively constant proportion of deaths caused by gases and vapors. Thus, pesticides cause an annual death rate in the United States of about 1 per 1,000,000 population.

Increases in the use of the newer pesticides, both in absolute tonnage and in relation to the older compounds, have added to their relative importance as causes of mortality. However, at least as late as 1956 and probably at present, over half the deaths associated with pesticides were caused by compounds older than DDT. Furthermore, over half the deaths are in children. These facts suggest that improvement could be made in the record if old poisons were used with the same care as new ones, and if all poisons - old and new - were stored under lock and key and then used in such a way that children could have no significant exposure to them.

The conditions of use may be just as important as the toxicity of a compound in determining its hazard. Aspirin is far less poisonous than parathion; yet it is a more important cause of death because it is so much more widely distributed and so often is stored carelessly. Children have a far greater opportunity to find and swallow a fatal dose of aspirin than any dose of parathion.

Morbidity from Pesticides in the United States

In this country all deaths must be reported, irrespective of their cause. Unfortunately, this is not true for nonfatal illnesses, including those caused by poisoning. Therefore, the number of cases of nonfatal poisoning must be estimated from the ratio of nonfatal to fatal cases found in special studies. There were from 25 to 115 nonfatal cases of poisoning for each fatal case in different years during 8 years of experience in one major city. Records of poison control centers frequently reveal a ratio much greater than 100 to 1, but less than 10% of the cases reported to them are hospitalized, and as many as 70% show no symptoms of illness. The most accurate estimate at this time, then, is that only one of about 100 cases of significant poisoning is fatal.

In most instances poisoning in man is clinically similar to poisoning in experimental animals. Animal studies have provided much valuable information, but have their limitations. The common laboratory animals are more susceptible than man to poisoning with some compounds, but less susceptible with others. The dynamics of storage may be different in animals and man.

Time will not permit us to explore the clinical aspects of poisoning by pesticides, but we should note that at least 49 different materials have produced human cases. This number would be larger if the individual compounds of arsenic, for example, were counted separately.

Although the effect of both single and repeated doses of pesticides on people is rather well known, there can be no a priori assurance that at least a few people will not respond to a particular chemical with a pattern of illness different from that previously established. It is conceivable that there may be long-term effects in man even when it is impossible to demonstrate them in experimental animals during their entire lifetime. It is theoretically possible that a poison will precipitate or aggravate a bacterial or metabolic disease just as prolonged inhalation of granite dust promotes tuberculosis. Toxicologists are constantly alert to these possibilities, especially in regard to diseases of unknown origin and diseases of increasing incidence. For example, when it was suggested that DDT is a cause of poliomyelitis (4), the possibility was considered and the lack of evidence was noted. Needless to say, claims for this relationship were dropped, even from scare articles, when vaccines against poliomyelitis were developed.

No matter what the source of suspicion, it is the responsibility of professional toxicologists to explore each possibility. They have done this in the past, and the search will continue indefinitely. However, it is important to realize that there is no conclusive evidence that pesticides - old or new - are a cause of any disease except poisoning.

No discussion of mortality, or morbidity, or storage, or any other effect of chemicals is meaningful except in terms of dosage. The Committee on Pesticides of the American Medical Association (1) has reported that: "Any effects of repeated exposure would appear on the average most promptly, most frequently, most diversely, and most severely among persons whose exposure has been long and intensive." That is why some doubt is associated immediately with any case alleged to result from exposure that is trivial in comparison with what people ordinarily withstand without inconvenience.

Dependable information on tolerable - or intolerable - dosage may be obtained from study of (a) people with occupational exposure, (b) volunteers who agree to take known doses and undergo specified tests, and (c) - in the case of compounds used as drugs - patients treated for some medical condition. A number of pesticides have been studied in occupationally exposed workers, 9 in volunteers, and at least 9 in patients treated therapeutically. I have reviewed the information on dosage in a paper available from the Government Printing Office (9).

Toxicologists must keep in mind the possibility that the clinical effects of one compound may be enhanced by another. Often the degree of this potentiation is low; but Murphy and his co-workers (16) report that it exceeded 100 in animal experiments with malathion and triorthotolyl phosphate, a compound that is not a pesticide. Arterberry and his associates (3) have reported what apparently is the only known instance of a human pesticide poisoning suspected of being aggravated by a drug.

In addition to clinical illness, other effects of pesticides must be recognized. Walker and his associates (22) found DDT in every complete meal they analyzed in this country, but the concentration in the entire diet is so low that the average intake is only 0.184 mg. per man per day. Because DDT is so widely distributed in food, we at the Communicable Disease Center have made numerous studies of this compound and found it occurs also in the fat of almost everyone in the country (7, 11, 15, 19). In the general population, the average storage of DDT is about 5 ppm, and the concentration of all DDT-derived material expressed as DDT is about 12 ppm (11). Meat abstainers (11) and Eskimos (7) store less than the general population. On the contrary, agricultural applicators store about three times as much as the general population (11), and formulators may store more than 600 ppm of DDT and more than 1,000 ppm of DDT-derived material (10). Published results (10) show that men can eat DDT daily at a level approximately 200 times greater than that in the ordinary diet without showing any detectable clinical effect, but

of course, they store large amounts of the compound and its derivative, DDE, in their fat tissue. Ortelee (18) found that more than half of the people working for years in DDT-formulating plants excrete, and therefore absorb, DDT at a rate equal to or greater than that of men eating 200 times more DDT than people get from ordinary food. The formulators remained well according to their own evaluation, their work record, and medical examination.

It is a general principle of pharmacology that a steady state of storage is reached in connection with continued, tolerated intake of a drug or other chemical. Thus, after a period of adjustment, the daily excretion of the chemical becomes as great as the daily absorption. Surveys which we carried out in 1954-56 (11) and again in 1961-62 (20) showed that no change had occurred in DDT storage among people in the United States since 1950, when Laug and his co-workers (14) measured it for the first time. It is not known whether the storage of other compounds is at equilibrium, but a group of British scientists (13) and our own group (12) both have found that traces of dieldrin are stored in people without occupational exposure. My associates and I (12) found traces of BHC also. It seems likely that the storage of other stable compounds will be demonstrated as analytical chemical methods are improved.

Production of Pesticides

Because of their value in public health and agriculture, the production of pesticides has increased greatly. The present manufacture of synthetic ones in the United States is about twice as great as the production of all pesticides was in 1949. The development of newer materials has decreased but not eliminated use of older poisons, such as the arsenicals. Use of some of the newer materials, such as DDT, has continued to increase, while the production of other new materials, such as benzene hexachloride, reached a maximum and then decreased somewhat. The new poisons not only are numerous, but all of them of any importance are sold under many trade names. Over 57 thousand formulations are registered in the United States. Furthermore, poisons may be applied in a variety of ways, some of which were unknown only a few years ago. For example, over 6,000,000 acres of cropland in the State of California alone have pesticides applied to them by aircraft each year. I have discussed these and related facts in greater detail in a report published comparatively recently (8).

Injury from Pesticides in Other Countries

In spite of the extensive production of pesticides, they have a relatively good safety record in the United States, Canada, and the

United Kingdom. The record was not so good in some countries of Europe when parathion was permitted for household use. The difference is not necessarily related to technological advancement. Here again, is an example that the way in which a compound is used may be more important than its toxicity in determining danger.

In Japan, Namba (17) found that there were over 3,000 deaths from parathion alone during the 6-year period 1953 to 1958. There is some reason to suspect that the record may be even worse in certain developing countries where vital statistics are collected in only a fragmentary way or not at all. Certainly, there have been isolated reports of hundreds of cases of human poisoning in single outbreaks (6). Good labeling appears to be the most important single measure for promoting safe use by a literate population.

The Contribution of Pesticides to Health

DDT has contributed to the control of at least 27 diseases of man (21). An aggressive campaign against malaria in Greece reduced the number of cases each year from a million in 1938 to twelve hundred in 1958 (2). Many tropical countries with similar needs lack vigorous programs. This is unfortunate, because prevention of disease has not only saved lives, but also permitted economic development and achievement of a higher standard of living (21).

It is a tragic possibility that the safety record of pesticides may be poorest where the need to increase the use of these compounds is greatest. DDT is credited with eradication of malaria in the United States and Italy. But, the greatest threat of malaria has always been in the tropics. Leading agriculturists agree, as pointed out by Decker (5), that people of the United States could not be so well fed without the use of agricultural chemicals, and parathion is credited with eliminating starvation in Japan (17). But the need is more dramatically apparent in some developing countries where partial starvation is a present fact.

When other methods of controlling vector-borne diseases are developed - as they undoubtedly will be - care must be taken to test their safety, as well as their efficacy.

Methods of Improving the Safety Record

If the safety record of pesticides is to be improved, both in the developed and the developing countries, attention must be focused on real problems as determined by official vital statistics, by the reports of poison control centers, and by epidemiological studies. As we have seen, problems may not be identical in different countries.

Furthermore, there must be variation in the ability of different countries to divert technically trained personnel to these studies and related regulatory activities. Therefore, each country must examine its technical resources critically before charting its course.

There are three kinds of laws designed to minimize injury by pesticides: (a) labeling laws, (b) laws regulating residues on food, and (c) laws regulating use. I have given examples of these kinds of laws and reviewed them in a comprehensive paper already cited (8). To be effective, all these laws must be based on research showing that a practice is safe before it can be permitted. Most of the toxicological information required under these laws is based on animal experiments. Often somewhat greater account is taken of use experience in connection with laws that regulate use directly than in connection with the other two kinds of laws.

Without doubt, good labeling is the most important single step to the safe use of chemicals. Good labeling, in itself, will go a long way to promote proper use. If education does not suffice, direct regulation can restrict use of specified chemicals to people who are properly trained and equipped for the work. When necessary, medical supervision of workers may be required, and there are now specific laboratory tests that permit measurement and, therefore, regulation of occupational exposure to many pesticides. In many instances, there are also antidotes and other methods of treatment that can be used with great benefit if poisoning does occur.

Conclusion

The very existence of highly active compounds poses potential and often real problems. Our primary protection is based on the extensive animal experiments required under present law. However, ultimate assurance about human safety of a particular compound must come from study of people with intensive and prolonged exposure. Such studies should give adequate warning of even the slightest danger to people in the general population exposed to traces of the same compounds. Much research remains to be done. The professional toxicologist must stay alert to danger, no matter how remote. But the time has passed when it may be usefully said that little is known about the toxicity of pesticides, or that no legal control of their use exists, or that a wide variety of illnesses from which mankind has suffered for generations are now caused by the newer pesticides.

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Occurrence of Poisoning by Pesticides

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Because of the value of pesticides in agriculture [5] and in the control of at least 27 diseases as well as many pests of man,[19] their production has increased greatly. The present manufacture of synthetic pesticides in the United States is over 700 million pounds per year, twice as great as the production of all pesticides in 1949. The development of newer materials has decreased but not eliminated use of older poisons such as the arsenicals. Use of some newer materials is still increasing; use of DDT reached a maximum but has remained essentially stable for eight years; use of lindane reached a maximum in 1951 and then decreased. Thus, the "newer pesticides" present a changing picture from year to year. At present there are more than 650 pesticidal compounds of all classes, and at least 200 are of first-rate importance. Pesticides are sold under many trade names, and this may serve to confuse the physician who is called on to diagnose cases of poisoning. Over 57,000 formulations are currently registered in the United States. Furthermore, pesticides are applied in a variety of ways, some of which were unknown only a few years ago. For example, over 6,000,000 acres of cropland in California alone are treated with pesticides by means of aircraft each year. I have discussed these and related facts in greater detail in a report published comparatively recently.[12]

The very existence of highly active compounds poses potential and often real problems. This brief paper is concerned with the mortality, morbidity, storage, and other possible effects associated with pesticides, and with methods for limiting injury caused by them.

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Mortality

In the United States near the turn of the century, the mortality rate for all accidental poisoning was approximately four per 100,-

000 population. For the last 25 years the rate has been essentially stable at approximately two per 100,000 population. A little over half of these accidents are now caused by solids and liquids, and a little less than half are caused by gases and vapors. In different years deaths from pesticides have accounted for 7.8% to 12.8%, or an average of about 10% of deaths from all solid and liquid substances. Deaths caused by fumigants constitute less than 1% of the deaths caused by gases and vapors. Thus, pesticides cause an annual death rate in the United States of approximately one per 1,000,000 population. As already mentioned, the rate is subject to some variation from year to year. However, there has been no distinct trend toward an increase or decrease during the last 25 years. Specifically, there has been no change associated with the newer pesticides and their increasing use.

This does not mean that poisoning by pesticides is randomly distributed. As is true of poisoning by solids and liquids in general, poisoning by pesticides occurs predominantly in children. Furthermore, as late as 1956, more than two thirds of the deaths associated with pesticides were caused by compounds older than DDT, and this may still be true in the majority of cases. These facts suggest that the improvement in the safety record of chemicals that occurred between the early part of the century and 1939 could be continued. It would be necessary only that the old poisons be handled with as much care as the new ones, that all poisons be stored under lock, and that the poisons be used in such a way that children could have no significant exposure.

Some accidental poisoning in people old enough to be employed is clearly occupational, and some is clearly unrelated to any work situation. There remain other cases which are difficult to assign. Of the 59 deaths from pesticides that occurred in 1956 in persons 10 years of age or older, 52 were clearly not occupational, five were clearly occupational, and the remaining two could not be classified in this regard although they occurred in work situations. In this same study, it was found that 15.2% of the total cases in persons 10 years of age or older were in nonwhites, and an additional 13.6% were in persons with distinctly Spanish names. These percentages are higher than the corresponding percentages of these ethnic groups in the general population.

Morbidity

Information on morbidity is not gathered and recorded so systematically as that on mortality. The number of cases of nonfatal poisoning must be estimated from the ratio of nonfatal to fatal cases in special studies. There were 25 to 115 nonfatal cases of poisoning for each fatal case in different years during eight years of experience in one major city.[12] The records of poison control centers often show a ratio much greater than 100 to 1, but over 90% are unhospitalized and as many as 70% may show no symptoms of illness. In recent years the California State Department of Health has reported annually more than 900 cases of poisoning associated with occupational exposure to pesticides. The corresponding number of occupational deaths ranged from only zero to three for the same years. It is clear from the record that many of the nonfatal cases were so mild that they might not have been reported if they had not been covered by workers' compensation.

Severity of illness is obviously the chief variable leading to the very different estimates of the ratio of nonfatal to fatal cases; some investigators count every report as a case while others count only cases of significant illness. There may be other unrecognized variables, the importance of which may differ according to the age, ethnic group, occupational status, or other condition of a particular population. However, at the present time it appears that a ratio of 100 to 1 for the entire population is the most accurate estimate possible.

Storage

One clear effect of exposure to certain pesticides is their storage in the body; however, unlike mortality and morbidity, storage

does not necessarily imply any injury. Storage is related to dosage, of course, and a sufficiently high level of storage of any compound will be associated with injury. However, the study of storage at noninjurious levels can yield a great deal of information concerning the absorption of compounds by groups of people with different degrees of occupational, dietary, or other exposure.

The chlorinated hydrocarbon insecticides are the most chemically and metabolically stable of the newer pesticides. Some of them are stored almost as tenaciously as the heavy metals. Of these chlorinated compounds, DDT, BHC, and dieldrin have been found in the body fat of people in the general population whose only significant exposure to them in this country is dietary. In the most recent survey in this country, the storage of DDT in the body fat of such people averaged 3.9 ppm; and storage of all DDT-derived material, expressed as DDT, averaged 12.9 ppm. Repeated surveys have shown that there has been no significant change in the storage of DDT in people in this country since it was first measured in 1950.[16] Storage in the United States is slightly more than that in Canada [18] or most of Europe,[14,17] but it is about the same as that in Hungary [6] and—as shown by our current research—much less than that in the people of certain developing countries. In this country people who do not eat meat store less DDT than the ordinary population.[13] This difference is associated with the dosage of DDT and not with meat intake per se, for Eskimos eat large amounts of meat and fat but store less DDT than any other group studied in recent times.[9]

The average storage of BHC is 0.2 ppm in this country [4] and 1.19 ppm in France.[14] The average storage of dieldrin is 0.15 ppm in this country [4] and 0.21 in southern England.[15] It has only recently become possible to measure these compounds in the small amounts that occur in tissues. It seems likely that their storage, like that of DDT, has reached a steady state, but measurements in subsequent years will be necessary to be sure. It also appears likely that the storage of traces of other chlorinated hydrocarbon insecticides will be demonstrated as chemical methods are refined. At the present time the storage of any substantial amounts has been ruled out by studies already completed.[4,14]

Other Possible Effects of Pesticides

As described in another paper in this Symposium,[22] the clinical picture of poisoning by all the major pesticides is well established. The same is true for basic information on storage. Both poisoning and storage are dose-related. These facts do not exclude the possibility that individual pesticides or groups of pesticides may have effects not yet detected. It is the responsibility of the professional toxicologist to explore objectively any possibility of this sort, no matter how remote. For example, there are individual case histories that suggest that some pilots who apply various organic phosphorus insecticides by aircraft have suffered lapses of attention or judgment leading to accidents. Obviously, no conclusion can be reached from the individual cases because of their small number, the inherent danger of flying cropdusting aircraft, the factor of fatigue, etc. However, if these compounds do lead to lapses of attention or judgment, these effects should be dose-related and subject to objective study. It is possible, too, that apparent lack of judgment might be related to a lack of attention at a critical moment. It is now well known that sleep deprivation and many sedative drugs, as well as petit mal epilepsy, lead to lapses of attention while proper doses of certain stimulants improve attention. Standard methods for studying attention are available. These methods were used by Durham and his colleagues [10] to study people with different degrees of exposure to organic phosphorus insecticides. They found that lapses of attention do occur but apparently only in persons who have absorbed enough poison to show other ill effects at the same time. The experimental results suggest that pilots should stop flying at the slightest hint of illness. Apparently, this is done to some degree, for the rate of accidents associated with cropdusting did not increase from 1951

to 1959 [3] although the use of organic phosphorus compounds and the use of aircraft for cropdusting did increase during the same period.

Sometimes the satisfactory exploration of a possible relation between a chemical and an injury must await development of a laboratory method. Certainly, this is true regarding the epidemiologically established fact that certain drugs cause myelogenic blood dyscrasias and the suspicion that a few pesticides may rarely do the same thing.

Methods of Minimizing Injury

A few remarks on methods for minimizing injury from pesticides seem appropriate even though a complete discussion is beyond the scope of this paper.

It is astonishing to see how few people are aware of the extensive regulations under which pesticides are sold and used. The laws are of three types: (1) laws regulating labeling through a system of registration, for example, The Federal Insecticide, Fungicide, and Rodenticide Act of 1947 as amended [20]; (2) laws regulating residues through a system of tolerances, for example, The Federal Food, Drug, and Cosmetic Act of 1938 as amended [21]; and (3) laws regulating use directly, for example, the licensing of operators [11] and also the Agricultural Code of California Relating to Use and Application of Injurious Materials.[2] There can be no doubt that wise administration of these types of laws at the federal and state level is responsible for the relatively good safety record of pesticides in this country. The special importance of good labeling has been pointed out.[12]

Under any circumstances the proper drafting and administration of regulations must be based on adequate technical information. This fact is particularly obvious in connection with occupational medicine and hygiene. Satisfactory methods of study have been established for many years for the dusts, fumes, and vapors that enter the body principally through the respiratory tract. The development of compounds that may be absorbed through the skin to a significant degree have required new methods of study. Progress made in connection with measurement of pesticides, many of which are absorbed through the skin, has been reviewed by Durham and Wolfe.[7,8]

Different routes may be important in the absorption of the same compound depending on the formulation and mode of use. Deposits of a chemical that may be absorbed through dermal contact may never have been airborne. For this reason alone, direct and indirect methods of measuring dermal exposure and absorption are required. Measurement of air concentration of chemicals is no longer enough. By the same token, threshold limits based on air concentrations may be of only limited value in connection with chemicals absorbed through the skin. There is now a growing interest in biological threshold limits based on measurement of chemicals or their metabolites in blood or urine. Such measurements are advantageous because they (1) indicate absorption from all portals without distinction, (2) ignore exposure that does not lead to absorption, and (3) have the potential to indicate absorption for an entire day or a selected part of a day. The fact that the use of biological threshold limits has proved difficult—for example, in connection with mercury [1]—brings us face to face with our ignorance of the dynamics of storage and the need for further research.

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Experiences with the Exposure of Human Subjects to Agricultural Chemicals and a Discussion of the Legal Position of Investigations Using People

PUBLICATION
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Introduction

In promoting human safety, the basic reason for making studies in man is species difference. Differences in toxic as well as therapeutic effects frequently depend on differences in biotransformation, which are well documented and may be qualitative (Williams, 1963), quantitative (Brodie, 1964), or both. Undoubtedly, only a small proportion of the true variation has been described. The facts that man is unique and that studies in man are desirable are taken as axiomatic in this paper. The body of the paper is concerned with the organization and execution of studies in volunteers and with the legal implications of such studies.

Although this paper is concerned with the broad subject of studies with volunteers, many of the illustrations used in the first section are, for convenience, drawn from our own experience, which may be summarized as follows: It is necessary to have a clear picture of the safety of a compound if it is to be used to combat human disease. This is equally true whether the compound is a drug administered directly to the patient or a pesticide applied to his environment. Some of our studies have concerned compounds proposed for use (Durham *et al.*, 1959; Hayes *et al.*, 1960; Rasmussen *et al.*, 1963; Witter *et al.*, 1961) or actually in use (Hayes *et al.*, 1956) for the control of vector-borne disease. Other studies concerned compounds that were especially adapted for studying a fundamental property of an important group of pesticides (Fredriksson, 1961a,b; Upholt *et al.*, 1956).

Our own work constitutes only a small portion of the investigations of pesticides that have been carried out with volunteers (see Table I).

TABLE I
STUDIES OF PESTICIDES IN VOLUNTEERS

Pesticide[a]	Parameter or condition[b]	References
Organic phosphorus insecticides		
DDVP	Cholinesterase	Durham *et al.*, 1959; Witter *et al.*, 1961; Rasmussen *et al.*, 1963
	Visual and respiratory functions, reaction time	Rasmussen *et al.*, 1963
	Function of sweat glands	McLaughlin and Sonnenschein, 1960
Demeton (Systox)	Cholinesterase	Upholt *et al.*, 1954; Rider and Moeller, 1960, 1964; Moeller and Rider, 1959, 1962b, 1963
DFP	Cholinesterase	Leopold and Comroe, 1946; Comroe *et al.*, 1946b; Rowntree *et al.*, 1950; Munkner *et al.*, 1961; Grob *et al.*, 1947a
	Intestinal mobility	Grob *et al.*, 1947b
	Mental effects in normal people and psychotic patients	Rowntree *et al.*, 1950
	Central nervous system effects	Grob *et al.*, 1947c
	EEG	Grob *et al.*, 1947c; Rowntree *et al.*, 1950
	Neuromuscular function	Harvey *et al.*, 1946, 1947
	General systemic effect	Grob *et al.*, 1947a
	Visual functions	Leopold and Comroe, 1946; Scholz and Wallen, 1946
	Myasthenia gravis	Harvey *et al.*, 1946, 1947 Comroe *et al.*, 1946a,b; Grob *et al.*, 1947a; Gaddum and Wilson, 1947; Buchthal and Engback, 1948
	Glaucoma	Comroe *et al.*, 1946b; Marr, 1947; Leopold and McDonald, 1948; Grant, 1950; Stone, 1950
	Abdominal distention	Grob *et al.*, 1947b
Diazinon	*Creeping eruption*	Hayes, 1963, p. 30;
Dimefox	Cholinesterase	Edson, 1956; Edson *et al.*, 1964
Dimethoate	Excretion, cholinesterase	Sanderson and Edson, 1964
Dioxathion (Delnav)	Cholinesterase	Frawley *et al.*, 1963
EPN	Cholinesterase	Rider *et al.*, 1959; Moeller and Rider, 1959, 1962a; Rider and Moeller, 1960
HETP	*Myasthenia gravis*	Westerberg and Luros, 1948
Malaoxon	Function of sweat glands	McLaughlin and Sonnenschein, 1960

TABLE I (*Continued*)
STUDIES OF PESTICIDES IN VOLUNTEERS

Pesticide[a]	Parameter or condition[b]	References
Malathion	Cholinesterase	Golz, 1959; Gutentag, 1959; Moeller and Rider, 1959, 1962a; Rider *et al.*, 1959; Hayes *et al.*, 1960; Mattson and Sedlak, 1960; Rider and Moeller, 1960
	Excretion	Hayes *et al.*, 1960; Mattson and Sedlak, 1960
	Pediculosis	Cole *et al.*, 1958; Barnes *et al.*, 1962; Shawarby *et al.*, 1963
Methyl demeton	Cholinesterase	Klimmer and Pfaff, 1955
Methyl parathion	Cholinesterase	Moeller and Rider, 1959, 1961, 1962b, 1963; Rider and Moeller, 1960, 1964
Naled (Dibrom)	Dermatitis	Kohn, 1962
Paraoxon	Function of sweat glands	McLaughlin and Sonnenschein, 1960
Parathion	Cholinesterase	Edson, 1957; Rider *et al.*, 1958; Rider and Moeller, 1960; Moeller and Rider, 1961; Funckes *et al.*, 1963; Hartwell *et al.*, 1964; G. R. Hayes *et al.*, 1964; Edson *et al.*, 1964
	General systemic effect	Goldblatt, 1950
	Absorption	Fredriksson, 1961a,b
	Excretion	Funckes *et al.*, 1963; Hartwell *et al.*, 1964; G. R. Hayes *et al.*, 1964
Schradan (OMPA)	Cholinesterase	Edson, 1955; Edson *et al.*, 1964
	Myasthenia gravis	Rider *et al.*, 1951; Gregory *et al.*, 1952; Schulman *et al.*, 1953; Osserman and Kaplan, 1954; Rider and Moeller, 1960; Hayes, 1963, p. 39;
TEPP	Cholinesterase	Grob and Harvey, 1949; Upholt *et al.*, 1956
	Symptomatology	Grob and Harvey, 1949
	Visual effects	Grant, 1948; Marr and Grob, 1950; Upholt *et al.*, 1956
	Myasthenia gravis	Burgen *et al.*, 1948; Grob and Harvey, 1949; Stone and Rider, 1949; Rider and Moeller, 1960
	Glaucoma	Grant, 1948, 1950; Marr and Grob, 1950

TABLE I (*Continued*)
STUDIES OF PESTICIDES IN VOLUNTEERS

Pesticide[a]	Parameter or condition[b]	References
Trichlorofon (Dipterex)	Cholinesterase	Lebrun and Cerf, 1960
	Symptomatology	Cerf *et al.*, 1962
	Helminthiasis	Beheyt *et al.*, 1961; Cerf *et al.*, 1962; Talaat, 1964
Carbamate insecticides		
Baygon (Bayer 39007)	Excretion	Dawson *et al.*, 1964
Carbaryl (Sevin)	General systemic effect	Hayes, 1963, p. 44
Chlorinated hydrocarbon insecticides		
Aldrin	Symptomatology	Baker *et al.*, 1959
DDD	Skin irritation, sensitization	Haag *et al.*, 1948
	Cushing's syndrome	Sheehan *et al.*, 1953; Southren *et al.*, 1961; Wallace *et al.*, 1961; Weisenfeld and Goldner, 1962
	Adrenal tumors	Molnar *et al.*, 1961; Nichols *et al.*, 1961
	Metastatic carcinoma, especially of prostate and breast	Zimmermann *et al.*, 1956; Weisenfeld and Goldner, 1962
	Diabetes	Törnblom, 1959
DDT	Symptomatology	Domenjoz, 1944; Neal *et al.*, 1944; Cameron and Burgess, 1945; Case, 1945; Dangerfield, 1946; Velbinger, 1947a,b; Stammers and Whitfield, 1947
	General systemic effect	Neal *et al.*, 1944, 1946; Cameron and Burgess, 1945; Case, 1945; Velbinger, 1947a,b; Stammers and Whitfield, 1947
	Sensitization	Draize *et al.*, 1944; Wasicky and Unti, 1944; Cameron and Burgess, 1945; Wigglesworth, 1945; Chin and T'ant, 1946; Haag *et al.*, 1948
	Storage	Hayes *et al.*, 1956
	Excretion	Neal *et al.*, 1946; Hayes *et al.*, 1956
	Pediculosis	Domenjoz, 1944; MacCormack, 1945; Kaiser, 1946; Zein-El-Dine, 1946
	Scabies	Zein-El-Dine, 1946
Dieldrin	Skin irritation, sensitization	Suskind, 1959
	Absorption, excretion, and concentration in blood	Abery *et al.*, 1959

TABLE I (*Continued*)
STUDIES OF PESTICIDES IN VOLUNTEERS

Pesticide[a]	Parameter or condition[b]	References
BHC and lindane	Symptomatology	Batterman, cited by Halpern *et al.*, 1950
	Skin irritation, sensitization	Halpern *et al.*, 1950
	Pediculosis	Cannon and McRae, 1948; Gardner, 1958
	Scabies	Cannon and McRae, 1948; Wooldridge, 1948; Halpern *et al.*, 1950
Perthane	*17-Hydroxycorticosteroids and clinical effect in tumor patients*	Talinferro and Leone, 1947; Weisenfeld and Goldner, 1962
Toxaphene	Symptomatology and general systemic effect	Keplinger, 1963
Mixture of lindane and DDT	Symptomatology	Baker *et al.*, 1959
Chlorinated hydrocarbon fumigants		
Carbon tetrachloride	Concentration in blood, urine, and expired air	Stewart *et al.*, 1961a
Tetrachloroethylene	Concentration in blood and expired air	Stewart *et al.*, 1961b
	Symptomatology	Rowe *et al.*, 1952
1,1,1-Trichloroethane	Concentration in blood and expired air	Stewart *et al.*, 1961c
Trichloroethylene	Excretion in urine	Souček and Vlachová, 1960; Bartoníček, 1962; Bartoníček and Teisinger, 1962
	Concentration in blood	Bartoníček, 1962; Stewart *et al.*, 1962
	Concentration in saliva and sweat	Bartoníček, 1962
	Concentration in expired air	Stewart *et al.*, 1962
Botanical insecticides and synthetic analogs		
Barthrin	Primary irritation, sensitization, and allergic response	Ambrose, 1963
Derris	Dermatitis	Ambrose and Haag, 1936
Pyrethrum	Dermatitis	Feinberg, 1934; Lord and Johnson, 1947; Martin and Hester, 1941
	Scabies	Sweitzer and Todder, 1935
	Intestinal helminthiasis	Chevalier, 1930

TABLE I (*Continued*)
STUDIES OF PESTICIDES IN VOLUNTEERS

Pesticide[a]	Parameter or condition[b]	References
Miscellaneous insecticides		
Azoxybenzene	Symptomatology	Faker *et al.*, 1959
DNOC	Concentration in blood and excretion in urine	Harvey *et al.*, 1951
Isobornyl thiocyanoacetate (Thanite)	Excretion, primary irritation, sensitization effects, and symptomatology	Keplinger, 1963
Rodenticides		
Thallium	Distribution and excretion	Farelay *et al.*, 1953
Warfarin	*Thromboembolic disease*	Shapiro, 1953; Pollock, 1955; Friedman, 1959; Wolff *et al.*, 1953; Clatanoff *et al.*, 1954; Paer *et al.*, 1958; Fremont *et al.*, 1963
Herbicides		
2,4-D	*Coccidioidomycosis*	Seabury, 1963

[a] Identification of the compounds listed can be found in the "Pesticide Index," edited by D. E. H. Frear (College Science Publishers, 1963).
[b] Therapeutic studies in volunteers are italicized.

Some of the volunteers were normal subjects who contributed to an understanding of the pharmacology of a pesticide. Others were patients who received the compounds identified as pesticides for treatment of disease (indicated by italics in Table I). However, in many of these latter instances observations were made that are applicable not only to the patients but to healthy people also. Although it is a fine point, the table omits studies of patients treated with compounds well recognized as drugs at the time they were studied even though the compounds are, *inter alia*, pesticides. Examples include quantitative studies of the toxicity of white phosphorus (Magnus, 1914), arsenic trioxide (Sollmann, 1957), and thallium compounds (Munch, 1934). The table also excludes studies of people with occupational exposure to pesticides even though success in such work usually depends on the subjects' voluntary cooperation.

Information on the effect of pesticides on man, whether obtained by study of volunteers or workers or cases of poisoning, is the subject of another paper in this series (Durham, 1965).

Practical Considerations

Parameters for Study

In planning any study with human subjects, provision must be made to examine every parameter known to be affected in animals exposed to harmless doses of the same compound. The first parameter to be considered is measurement of the compound under study: Is it absorbed at all? If absorbed, how is it distributed in the body, and how is it excreted? How much of it is stored and for how long? These questions are related to a second parameter, the metabolism of the compound within the body: Is the compound altered in any way? If so, what are the biotransformation products? Is the material excreted as a conjugate?

A third parameter involves enzymes, especially those which occur in the blood and which are known to be affected by subclinical doses of some drugs or other chemicals, for example cholinesterase (Holmstedt, 1959) or serum alkaline phosphatase (Mountain, 1960). In a similar way, elevation of neuraminic acid in the serum (Stokinger and Wagner, 1958) and decrease of cystine in the fingernails (Mountain *et al.*, 1955) have been demonstrated in the absence of illness in persons exposed, respectively, to vanadium and cobalt. Finally, a whole series of physiological functions such as taste, odor, visual acuity, complex reaction time, or airway resistance may be explored. As already suggested, the exact choice of tests will depend on the results of earlier animal studies, but it may depend also on functions considered critical to persons (e.g., pilots) who may use the material to be studied.

Certain sensitive criteria such as depression of growth rate or altered ratios of organ to body weight cannot be explored in man. However, the fact that human subjects can communicate makes it possible to study many parameters that may be altered in animals, but not in a way that the experimenter can detect. For example, depth perception in monkeys would probably be impaired by unilateral miosis caused by tetraethyl pyrophosphate, just as it is in man (Upholt *et al.*, 1956). However, any experiment designed to detect alteration of depth perception in monkeys would be so complex that it would be difficult to interpret the results—much less to extrapolate them to people.

In addition to the special studies just mentioned, there must be a general surveillance of the subjects of the sort ordinarily involved in hospital admission. Thus, there must be a history and physical and clinical laboratory examinations. These studies must be repeated at suitable intervals, partly to determine whether any dose-related change is occurring that was not predicted by animal studies. One should always

be alert to the possibility of sensitization. The same examinations serve to reveal illnesses which, though basically unrelated to the chemical under study, may nevertheless affect the response of the body to it or merely serve to confuse the results.

Selection of Dosage

The highest dosage selected should be one which is believed to be (a) harmless on the basis of animal studies and all other available information, and (b) capable of influencing some measurable parameter. For compounds of low toxicity, measurement of excretion of the compound or its metabolites may be the only parameter influenced. For compounds of moderate or high toxicity, it may be desirable to use a graduated series of doses beginning with a very low one. Regardless of the toxicity, it is usually desirable to have more than one dosage either in a single test or in succeeding tests in order to determine whether responses are dose-related. Even if dose response is not under investigation, it is necessary that a control group be included in every study. Its use may serve to detect laboratory error and other factors that might influence the results without having any relation to the agent under study.

In connection with agricultural chemicals, the highest dosage chosen for study in volunteers is frequently less than that absorbed by some men with occupational exposure. It is seldom practical to continue a study of volunteers for as many years as occupational exposure may last. Thus, study of people with heavy occupational exposure is more likely to reveal whether the chemical influences conditions that occur spontaneously in its complete absence. Studies in workers may reveal effects that would never be detected in the general population subject to only minor exposure. Of course, the occurrence of some ill effect among workers does not necessarily mean that the same effect will occur among persons with only a fraction of their exposure. However, the finding of an effect among workers is a warning of effects that may occur in a few sensitive people, generally after a very long period of continuous, though limited, exposure.

Although studies in volunteers are limited in dosage and duration, these defects are compensated by the important fact that the dosage and route of exposure are known exactly. Thus, studies with volunteers may make it possible to estimate the amount absorbed by men under occupational conditions. For example, Ortelee (1958), basing his extrapolation on a study of volunteers, was able to conclude from a study of excretion that the average quantity of DDT absorbed by formulators with maximal exposure to the compound was approximately 42 mg/man/day.

Thus, studies both on volunteers and on persons with heavy occupational exposure have special merits, and neither can fully replace the other. This paper is concerned only with studies on volunteers, but some of the matters discussed have application in studies of people with occupational or other special exposure to chemicals.

Choice of Subjects

The choice of subjects for a study is determined by the number of people required and the duration of the work. It is practical to use civilian subjects for investigations requiring a small number of persons, relatively brief sessions of participation, and a short overall duration. Institutional subjects are necessary when relatively large groups must be used in order to ensure significant results or when frequent or prolonged participation is essential. For example, such a simple thing as oral administration of a drug 7 days a week for a year becomes complicated except in an institutional situation. Business trips, vacations, or the demands of home or business will interfere with daily participation by the ordinary civilian. Even worse, these factors will interfere with the civilian volunteer's recording of his activities related to the investigation. Of course, there will be missed doses and other lapses in an institutional setting, but it is easier to ensure faithful participation and, especially, complete recording in an institution.

No absolute rules can be laid down to distinguish studies that will be successful in a civilian setting and those requiring institutional organization. Our own studies with civilians have lasted no more than a few weeks. In some of these studies some volunteers participated for less than half a day on a single occasion and yet made a valuable contribution. We have never used civilian volunteers for a study requiring surgical biopsy or any other procedure that would require subsequent medical attention or even inconvenience to the person at the end of the working day. This does not mean that biopsies might not be practical in some studies of civilians.

Our own studies in institutions have scheduled the participation of individual volunteers for periods as short as 8 weeks and as long as 4 years. Actual participation has frequently exceeded the schedule. Seventeen men participated 5 years in a study of the storage of DDT originally scheduled for 4 years. Furthermore, some of these studies in institutions involved biopsies, which, of course, left small permanent scars. Some studies carried out by others have required the production of serious disease in the volunteers. Most, and perhaps all, such studies were done under institutional situations that permitted hospital care of the volunteers for whatever period was required. Examples include studies of

antimalarial drugs (Coatney *et al.*, 1953) and of the transmission of yellow fever (Reed *et al.*, 1911). In the first instance, a meaningful study of drugs required that men who had never had malaria must be infected with recognized laboratory strains of it under standardized conditions. In the second instance, the transmission of yellow fever to man was the question under investigation.

Our own studies of civilians have included laboratory personnel, men who had a special interest in a study directly related to their occupation, and, finally, people whose only motivation was an interest in science. All our institutional studies have been carried out in federal prisons. In addition to federal prisoners, others have used state prisoners (Goldberger, 1916), military personnel (Reed *et al.*, 1911), conscientious objectors, students (Winkelstein *et al.*, 1962), and hospital patients (Steiner *et al.*, 1962). It is clear that the suitability of each class will vary for any particular study.

Minors, incompetents, or married women should not be accepted as subjects, except perhaps for therapeutic or diagnostic studies, because they may be unable to enter into a valid contract.

Protocol for a Study

Every study involving people should be carefully planned in advance. Before a written plan is drawn up, an informal agreement should be reached with the administration of any institution where a study is to be made. However, the plan should be documented even in those instances in which a written protocol is not required as a basis for approval by (a) custodial authorities, for administrative feasibility; or (b) academic or comparable authorities, for scientific merit and safety. The protocol should cover at least the following topics: (1) account of the problem and justification of the study; (2) specific purpose of the study; (3) experimental design; (4) safety of the study; (5) reward to volunteers; (6) proposed contract.

The "problem" referred to in item (1) above is the underlying condition that justifies the study. For example, the problem may be a mosquito-borne disease for the control of which a pesticide is proposed. The importance of the disease will be a significant factor in determining whether a study is justified. As another example, the problem may be an observed condition such as air pollution or factory noise or the need to use a pesticide in agriculture.

The "problem" may be large and even ill-defined, but never unimportant. By contrast, the purpose of any study with people should be clearly defined and frequently very limited. Thus, study of a drug to

treat hypertension might be limited to investigation of the metabolism of safe doses in normotensive and hypertensive men.

The section of the protocol dealing with experimental design should state the number of volunteers to be studied and outline their distribution into control and experimental groups. The rate and duration of dosage should be given, and the predosage and postdosage observation periods should be defined. The study need not be confined to a preestablished interval, but may be planned to continue after the dosage period until some parameter (e.g., excretion of a metabolite of a drug) has reached a predetermined level (e.g., the same level found in controls). The section on experimental design should give particular attention to those things that will concern the volunteers directly. It is necessary to specify the approximate number and extent of blood samples, surgical biopsies, and other procedures to be carried out that may involve pain or risk. It is equally necessary to describe procedures that involve merely inconvenience or interference with institutional routine. We have never had any administrative difficulty with biopsies, but we almost lost an entire project because the way in which timed urine samples were collected interfered with the employment of a few of the volunteers in a weaving mill, which was a part of the occupational training and therapy program of the prison. Fortunately, it was possible to change the schedule for collecting samples without decreasing their number or value, and the study was saved. Not all difficulties can be foreseen, but they can be reduced by careful planning.

The section on safety is one of the most important parts of the protocol. Ideally, the section is brief and depends for depth on one or more supporting documents, constituting an appendix. Regardless of the form of presentation, the section must define the nature of any possible hazard, the probability of danger, the surveillance available to detect or—if possible—predict injury, and the possibility of specific treatment. Finally, it must state that individual volunteers or the entire group will be withdrawn from dosage or other active participation if circumstances require this action. Of course, a volunteer whose dosage is stopped will continue under observation, and he will be treated if necessary.

The protocol should specify the rewards (e.g., money) that the investigator is prepared to give volunteers. It may also propose other rewards (e.g., reduction of prison sentence) that would be appropriate and desirable but are not under the control of the investigator.

The final section of the protocol should refer to a proposed contract, offered as an appendix. The contract should be written in the first person, for each volunteer to sign. It is my impression that release forms similar

to those used for diagnostic and surgical procedures in hospitals are frequently used in connection with investigations with civilian volunteers, and the American Medical Association (1961) has supplied a model release form (Form 29) for use with investigational drugs. We have used simple releases for civilians. On the contrary, our contracts for studies in institutions have been more elaborate. They include the following features:

(a) date
(b) name of organization (or person) making the study
(c) name of institution where study is made
(d) name of applicant
(e) description of the study
(f) kind and approximate number of services applicant will be expected to contribute and the approximate duration of service
(g) statement by the applicant that the procedure, value, and danger of the study have been explained to him and that he is fully aware that there can be no guarantee that he will not become ill (in a study in which illness is really anticipated, its nature should be defined in the contract)
(h) statement by the applicant that he knowingly and voluntarily accepts the risks, and agrees to cooperate in the work
(i) amount of money and other rewards the applicant will receive in exchange for his services, provided his participation is satisfactory
(j) applicant's statement on behalf of himself, his representatives, and heirs that he releases the investigators and the organization they represent from all liability, including claims, and suits at law or in equity for any injury, fatal or otherwise, that may result from his participation in the investigation
(k) signature of the applicant
(l) signature of witnesses
(m) signature of responsible investigator who accepts the applicant as a volunteer
(n) signature of officer who approves contract for the institution where the work is done

Note: The contract omits any statement that the applicant agrees to remain in the project.

Method of Obtaining Volunteers

The method of obtaining volunteers varies with circumstances. In an institution, the best way to begin is for the administration to issue a general notice—in the form of an announcement at general assembly, a statement over the public address system, a poster, an article in the institution's newspaper or newsletter, or a mimeographed handbill issued to all personnel. Such a notice should state the purpose and nature of the study very briefly and invite anyone interested to attend a meeting at which further explanation will be offered. In the notice, it is best not to mention the number of volunteers needed, because a small number may discourage some people from further inquiry. If possible, the

custodial staff of a prison should screen those who propose to attend an introductory meeting, to exclude those who are unsuitable. For example, some prisoners with a 6-month sentence will not hesitate to volunteer for a 5-year study.

At the meeting, the principal investigators (and perhaps others) explain the proposed study, placing special emphasis on: (a) the value of the work; (b) what each volunteer will be asked to do; and (c) the hazards—no matter how remote—that the volunteers may encounter. Of course, the rewards, the contract, and the other administrative arrangements also should be explained. Questions from the audience are answered. The audience is then asked to express its interest in participation. A list is made of those who wish to apply, and they are instructed when and where to go for preliminary examination.

Before the medical examination is actually carried out, the custodial authorities should screen the applicants to exclude those who are known trouble-makers, malingerers, psychotics, or custodial risks.

A complete history as well as appropriate physical and laboratory examinations must be done on each applicant. Special laboratory tests may be indicated, depending on the nature of the study. All the examinations may serve to exclude some applicants from the study, and all are used as a baseline for judging future findings in the others.

Those who are found satisfactory for the work are then asked to sign the contract.

Motivation of Volunteers

Factors that may play a part in motivating people to participate in projects include: (a) tangible rewards; (b) a desire for new experience; (c) occupational or other interest in a specific project; (d) interest in science generally; and (e) a desire to contribute to society.

Tangible rewards include money and (in the case of prisoners) reduction of prison term. The reduction may be guaranteed and prorated according to the duration of participation in the project, or it may be merely potential—a hope that participation will influence parole or the dropping of detainers by another court. Persons who have no direct experience with human studies often assume that need for money or desire for a reduction in prison term are major factors in the motivation of volunteers in prison. This may be true in some instances. We have always paid prisoner volunteers, but the amount of money was so small that it is probably not an important factor in motivation, and some civilians were not paid at all. We have recruited prisoner volunteers without difficulty when no reduction in prison term could be offered.

Probably the most general reason people have for participating in

studies is a genuine interest in science. People want to help in solving any problem they understand.

Prisoners share an interest in science with people in general. However, many prisoners have a special, often unrecognized urge to do something useful. They wish to compensate for records indicating little contribution to society and little positive attention from society. They want to contribute as well as to be recognized. Few prisoners will admit this except, perhaps, in time of war, when any worthwhile act can be attributed to patriotism. Even though prisoners deny it, I believe that an urge to serve society is their most important single motivation for participating in projects.

Miscellaneous Remarks

In our studies, volunteers are free to stop their participation at any time. The number of dropouts (exclusive of transfers and paroles) has been inversely proportional to the amount of initial screening. We have had more applicants for each project than we could accept. However, in only one instance were there so many applicants that we could practically dare them to withdraw; the men who were finally accepted were of such character that none dropped out during the entire project. In studies in which only a few applicants were excluded, a few dropouts occurred for no apparent reason, usually very early in the program. One man quit after the first biopsy (Hayes *et al.*, 1956). Once a project has settled down to a routine, it is most unusual for a volunteer to drop out. Even the few who for a time considered that a transient illness was related to their dosage were willing to continue participation and accept our judgment that no relationship existed. Of course, they were more assured when the illness resolved.

In studies such as those on antimalarial drugs, in which production of the disease was a necessary part of the work, the men accepted their illness with true heroism.

Although volunteers should be told the complete design of the study, it should be a part of the agreement that no volunteer is told the dosage group to which he belongs. A device we have used to avoid errors is to give placebos to all dosage groups for about a week at the beginning of a study. It is entirely natural that people should be apprehensive when they start a project. Ideas circulate among them by suggestion. We have had those who thought they had improved appetite and felt better, as well as those who lost appetite and felt worse while taking placebos.

If volunteers know there is a control group but have no hint of who is in it, many of them tend to complain less, because they realize they

may be in that group from whom a complaint would be evidence of weakness or neurosis. Of course, the controls do complain just as often as others. Among the most extensive complaints we ever received came from a man who had taken only placebos. Rather than merely refusing a biopsy he did not wish to take, he reported that he was generally unwell. As examples, he mentioned dermatitis and a febrile illness, for which he was hospitalized for 1 day. He attributed all his troubles to participation in the project. Examination confirmed the dermatitis and some congestion of the nose, residual from the upper respiratory infection a week before, but offered no evidence of other illness (Hayes *et al.*, 1956).

Complaints are distinctly more frequent among certain highly emotional ethnic groups. However, others in these same groups are the ones most likely to express gratitude for the benefit they have received from the study.

In addition to tangible rewards, benefits may include a sense of accomplishment. One prisoner told me that participation in the project had led to his reinstatement in his family. His father was pleased that he had finally done something useful.

Legal Considerations

Outline of Present Thinking

Background information on investigations using human subjects has been reviewed at length elsewhere from various points of view (Anonymous, 1955, 1959; Beecher, 1959; Flood, 1955; Heger and Gloriaux, 1957; Herings, 1955; Ladimer, 1954, 1957; Larebeyrette, 1954; Markel, 1963; Thomson, 1955; Wiggers, 1950; World Medical Association, 1957). An anthology of papers on the subject, edited by Ladimer and Newman (1963), is available in book form. An editorial (Anonymous, 1959) published in the *Canadian Medical Journal* gave an excellent summary of present thinking and, incidentally, reflected some of the inconsistencies in that thinking. Some of the points raised by the editorial appear irrefutable. They may be rephrased as follows:

1. Scientific investigations on human subjects have been conducted since time immemorial.

2. In the past 20 years or so, for the first time, much attention has been given to a study of the ethical, moral, and legal implications of investigations on man. This has resulted, doubtless, not only from the growth of this field of medical endeavor but also from the widespread disgust at revelations at the Nuremberg trials after World War II.

3. It is agreed that man is the ultimate necessary test subject in many instances, and medical investigations with people are unavoidable.

4. Abuses of this type of research are likely to be due more to ignorance or thoughtlessness than to deliberate malice.

5. To keep investigations within permissible moral and ethical bounds, the first consideration is that the subject should give consent within the full legal meaning of that word.

The same editorial (Anonymous, 1959) states: "It is a curious fact that the legal profession seems to have taken little notice of human research so far." This statement seems to me to reflect a confusion that underlies the major difficulty medical scientists are having in reaching a satisfactory overall concept regarding such research. However, before undertaking any discussion of legal problems, it would be well to review the codes that have been proposed for the regulation of research on people.

Codes

Although they are not a source of law as it relates to liability, a number of codes are important for the guidance of investigations. After the hippocratic oath, which applies to medical investigations as well as to medicine in general, the best known of the formal codes is the famous Ten Points laid down by the Nuremberg Military Tribunal. These ten principles have been carefully considered from many points of view by Ladimer (1954, 1957), Beecher (1959), and others (American Medical Association, 1946; Flood, 1955; Guttentag, 1953; Ivy, 1948; Shimkin, 1953). They may be summarized as follows:

1. Voluntary consent of the subject is absolutely essential. Consent must be based on knowledge and understanding of the elements of the study and awareness of possible consequences. The duty of ascertaining the quality of consent rests on the individual scientist and cannot be delegated.

2. The test should seek some benefit to society unobtainable by any other method.

3. The investigation should be designed and based on prior animal study, the natural history of the disease or problem, and other data, so that anticipated results may justify the action taken.

4. It should be so conducted as to avoid unnecessary physical and mental suffering.

5. No test should be undertaken where there is reason to believe that death or lasting disability will occur, except perhaps where the investigator may serve as his own subject.

6. The degree of risk should never exceed that which the importance of the problem warrants.

7. There should be preparation and adequate facilities to protect the subject against even remote possibility of injury, disability, or death.

8. Only scientifically qualified persons, exercising a high degree of skill and care, should conduct investigations on human beings.

9. The subject should be permitted to end the test whenever he reaches a mental or physical state in which its continuation seems to him impossible.

10. The investigator must be prepared to end the test if he has reason to believe that its continuation is likely to result in injury, lasting disability, or death.

Additional guidance for human investigation as given by Beecher (1959), is provided by the following: (a) the Declarations of Geneva and Rome, each of which is essentially a rephrasing and amplification of the hippocratic oath; (b) pertinent statements from the French National Academy of Medicine, from representatives of the French Academy of Moral and Political Sciences, representatives of the Paris Hospitals, and from the chief of the French Army's central laboratory for bacteriology; (c) the British view as stated by a Briton acting as Special Consultant to the United States Public Health Service; (d) opinions expressed by Pope Pius XII; (e) the World Medical Association's presentation of a report from a study into all phases of human investigation; (f) Wigger's statements (1950); and (g) the expressed views of the U. S. Public Health Service and the American Medical Association. The most recent statements include that of the World Medical Association (1964) known as the Declaration of Helsinki and that of the Medical Research Council (1964). Some of the codes are less comprehensive than others, but in spirit they are all generally consistent.

Beecher (1959) observed that, in effect, the Public Health Service has adopted the Nuremberg Ten Points, with added comment on the importance of group review and group approval of all procedures where even remote possibilities for hazard exist. The American Medical Association (1946) also endorses the principles expressed in the Nuremberg Code. Succinctly put, to conform to the ethics of the Association, investigations on human subjects must meet three requirements: (1) There must be voluntary consent of the person on whom the investigation is to be performed. (2) The danger of each study must be previously investigated by animal experimentation. (3) The investigation must be performed under proper medical protection and management.

In an editorial summary (Anonymous, 1959) of Beecher's review

(1959), it was concluded that in the last analysis the moral and ethical standing of human investigation depends upon the good sense and integrity of the participating physicians, rather than on an elaborate code of ethics.

Necessity for Definition of Kind of Investigation

Much of the confusion that exists not only in popular concepts, but also in professional articles and reviews, about investigations on human beings would be minimized if a classification such as the one given in Table II or the one implicit in the most recent annual report of Britain's Medical Research Council (1964) were kept in mind. For example, it has been stated that use of the "hopelessly incurable" suggests that the

TABLE II
Classification of Investigations on Man

I. Investigational diagnostic procedures or therapy This class presupposes a calculated risk by the patient, who is sick at the time and who freely consents[a] to a new procedure in order to benefit his own health, but usually without any other reward. The following subdivisions may be recognized:	
1. Systematic[b] testing of new, animal-explored treatment in selected groups of patients	Examples: (a) test of pyrimethamine for malaria (Coatney *et al.*, 1953) and isoniazid for tuberculosis (Mount and Ferebee, 1952)
2. Opportunistic[b] use of candidate treatments previously explored fully in animals	Examples: (a) tests of rare surgery (Woodruff *et al.*, 1963); (b) tests of antidotes for poisons (Namba, 1961)[b]
II. Investigational physiology (*lato sensu*) This class presupposes a calculated risk by the subject who may be well, sick, or moribund at the time and who freely consents to a study without any hope of individual benefit to health but often for other rewards. The following subdivisions may be recognized:	
1. Systematic[b] testing of animal-explored phenomena in selected groups of subjects	Examples: studies of the safety of malathion (Hayes *et al.*, 1960); study of oxygen and carbon dioxide (Consolazio *et al.*, 1947)
2. Opportunistic[b] exploration of phenomena previously explored fully in animals	Examples: (a) study by Beaumont (1833); (b) a large portion of good occupational medicine

[a] In the case of patients who are unable to give consent because of their age or medical condition, consent should be obtained from the parents or next of kin, just as is true in connection with any diagnostic procedure or therapy for such patients.

[b] It should be noted that the difference between "opportunistic" and "systematic" study has no relation to the care with which the work is planned and executed but is determined by the frequency of suitable subjects available for study.

sicker a patient is, the less consideration he deserves from his physician. This notion is the direct result of confusing investigational *therapy* with investigational *physiology*. If the investigation involves a new therapy that the physician is fully capable of giving and that offers the patient his only hope of recovery, then the physician not only is justified in offering it to the patient, but is under some obligation to do so. If, on the other hand, investigation involves a physiological study and if the patient is capable of consent, then there is no reason he should not volunteer for such work, particularly if it is carried out by a qualified investigator other than his personal physician. By cooperation between the physician and the investigator, impairment of the relationship between the patient and his physician may be avoided, and yet the dying man may make a useful contribution to a study that might otherwise be impossible (e.g., a study of the distribution of a drug in all tissues, to be determined by analyses after death).

Legal Problems

The entire question of investigations on man has been greatly complicated by memory of what went on in Nazi Germany and by the fact that a large proportion of the strictly legal consideration of investigations on man has been concerned directly with the Nazi activity. The memory of the Nazi experiments is widespread and lasting, for they have been brought to public attention through all mass media by the Nuremberg trials and the Eichmann trial. The most obvious medical contrast between these experiments and legitimate investigations concerns the degree of danger to the subjects. The character of some of the tests excluded any possibility of voluntary participation, and the major legal contrast involves the coercion of the subjects. There can be no proper medical investigation of man without consent. Another contrast relates to the real need for using human subjects. Certain types of investigations cannot be advanced through animal studies (Jefferson, 1955; Ladimer, 1957), but most of the work done by the Nazi physicians could very well have been completed in lower animals.

A more subtle but probably more fundamental contrast concerns the freedom of the experimenters. The Nazi physicians were subject to political pressure and were under military orders to carry out the work. The personal guilt of the Nazis or the legal basis of their trial is not germane to this discussion. It is germane to observe that similar misuse of people has not occurred when investigators were free.

Let us now consider the legal status of new procedures that do fall within the tradition of medicine. Although history shows that human experimentation in medical science is as old as the medical profession

itself, courts generally have not wavered from their original stand that human experimentation is at the peril of those who conduct the tests. Ladimer (1957) cites English and American court cases going back to *Slater* vs. *Baker*, in the year 1767. In that case, under the English jury system, the fact was established that the physician lacked proper skill and failed to obtain the patient's consent in using a previously untested medical procedure. The case established a rule that has been followed in both English and American law, and, indeed, perhaps in much of the world.

A review of pertinent cases reveals that most litigation has been between a single physician and one patient. The unhappy patient has charged the physician with "experimenting," and the physician has denied the charge and set up a defense that the practice employed was: (a) of recent origin, successfully used elsewhere; (b) a rare procedure, previously tried with success by the physician and known to be sometimes used; or (c) proper in view of its comparability to similar accepted procedures.

Under such a defense an unfavorable verdict would be a finding of negligence (malpractice), and the true issue of investigation would not arise. Should a claim arise in the course of a planned investigation, the best defense is proof that the subject assumed the risk knowingly and voluntarily.

Because the word "experimentation" carries the legal implication of malpractice, it is only common sense to avoid its use in connection with proper medical investigation.

The inference from judicial opinions does not necessarily imply that well-planned, properly controlled, and carefully executed human investigation would result in liability of the physician, where consent was obtained and the study carefully explained to an adult capable of understanding the possible consequences. In fact, such investigation of new drugs is subject to extensive regulation under the Federal Food, Drug, and Cosmetic Act (1963).

The view cited above that it is curious that the legal profession seems to have taken little notice of human research is naïve. The legal profession has not traditionally regulated the other professions. The licensing of physicians and the regulation of their professional affairs is carried out by the *medical* profession under authority of legislation sponsored largely by the *medical* profession. Even the Ten Points laid down by the Nuremberg Military Tribunal are based on previously accepted medical views. On the other hand, it is one of the duties of the legal profession to adjudicate claims of injury no matter from whom

they arise. Thus, medical malpractice, whether experimental or not, is a natural concern of the legal profession because it gives rise to claims.

Practical Measures to Protect Investigators

Wiggers (1950) has proposed that investigations should be so conducted that legal liability under malpractice or personal injury laws "never comes into question." It is obvious that this represents the ideal situation, but equally obvious that there will be failures in the best laid plans of men. Over and above the scrupulous care that should be exercised in planning and carrying out any medical investigation on human beings, attention should be given to the inevitable *possibility* of claims growing out of the work.

Investigations should not be carried out without consent. The best way to establish the fact of consent is through a written statement or contract signed by witnesses as well as by the volunteer. The content of such agreements was outlined in the section "Protocol for a Study." While written consent will not protect the investigator against liability for his negligence, it will constitute a defense against claims for injuries resulting from foreseeable and assumed risks (Office of General Counsel, U. S. Department of Health, Education, and Welfare, December 1959).

Another important evidence of consent is the recognized ability of the volunteer to discontinue participation at any time, with or without reason.

The investigator or his organization should be in a position to underwrite the care of any injury that truly results from his investigation. This does not imply that the volunteer should be permitted to abuse the privilege by bringing claims for ailments quite unrelated to his participation in a project.

One way of meeting the obligations for justified care of the volunteer is through special insurance. In a study recently carried out by a private institute on the irritant effect of air pollution on the eyes, insurance for three million dollars was purchased for $278.90 (Zavon, personal communication to the author).

Ballard (1964) has discussed the possibility of legal and financial support from the manufacturer of a compound in the event that an authorized investigator of the compound is sued.

Another substantial evidence of support of medical research would be the passage by governments of malpractice tort legislation covering research as well as clinical practice for all professional health workers. A well-written law of this sort would, of course, require the consent of subjects and set other standards for conduct of investigations; com-

pliance with these standards would then place the health worker within the scope of his employment and the protection of the law. Willingness of the government to accept claims or to defend the employee in a suit not only would tend to protect the individual physician or scientist but —perhaps even more important—would be an evidence of good faith in medical practice and research.

Claims are less likely to be successful if the research is carried out by someone of standing and reputation. Review of the work by a recognized authority, group, or agency offers objective evidence that the project is justified and that it has been carefully planned. In view of the recognized value of medical investigations on human beings, there is a double obligation on the part of official medical associations, medical schools, and governmental health agencies. First, they should make sure that only proper investigations are carried out on human beings. When they have done this, and have given their permission for studies on people, they have a second and equal obligation to make it clear that their approval has been granted. Approval should not be a one-sided affair in which the group in authority reserves the right to prevent poorly conceived research but evades responsibility for the research it does permit. A letter signed by the president, dean, or other responsible officer of the authorizing agency should be in the hands of the chief investigator before the work is actually begun.

Leading national and international medical and health organizations have an obligation to make it clear by editorials or other public statements of policy that the organization does approve and does actively promote proper medical investigations on human beings. No doubt discussions must continue about the details of codes or criteria that already exist for the guidance of such investigations. In fact, the very existence of these discussions, coming as they do from leading research institutions such as the Medical Research Council (1964) and the World Medical Association (1964), is evidence for the firm position that investigations on people now hold in medicine. However, such discussions, no matter how desirable, do not take the place of clear official medical statements championing the kind of research that now, in fact, constitutes accepted practice.

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PB 275 974 PESTICIDE PUBLICATION

Pesticides and Human Health—A Query

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I have been asked to consider the relationship of the pesticide chemicals to human health. The title suggests that there is some question about the existence of a relationship. Certainly there is no question as to the propitious relationship between pesticides and human health. We have only to recall the phenomenal reduction of malaria throughout most of the world (1).[2] We can now effectively abort an encephalitis epidemic or stop a plague outbreak. We can now control pest insects such as moths, cockroaches, and house flies. The productivity of the agricultural industry has increased dramatically since the introduction and widespread use of pesticides. To the malnourished millions throughout the world this is perhaps the single most important factor in their future health and well being.

But what of the hazards to human health? The U.S. Public Health Service, by combining several ongoing programs in 1966, implemented a pesticides program designed to evaluate the risks to man of pesticide use. Our basic research program provides knowledge on chemical structure, toxicity, modes of action and methodology. We provide training to State health department personnel in the epidemiology of pesticide chemicals and in analytical methods used to detect and identify pesticides. A pesticides Abstract Bulletin is provided for those scientists interested in the public health aspects of pesticides. Our program, together with those of other government agencies, publishes a journal, The Pesticides Monitoring Journal, in which investigators may publish their data on levels of pesticides found in food, air, water, soil, and in human and animal tissues. A pesticide specialist is assigned to State health departments where that competence is not otherwise available. We also arrange to have postmortem samples of human tissues collected in most of the States, and our laboratories determine the levels of the organochlorine pesticides in these tissues.

The Community Studies Section operates 16 Community Pesticide Study projects by contract with State health departments and universities. Scientists in these projects are concerned with the amounts of various pesticides to which people are exposed, the effects of this exposure, and the importance of the observed effects upon the health of the individual. We are concerned with the ecological factors which may be important in determining the dose of pesticides a person receives and his response to that dose. We are interested also in potentiation of effect by drugs or interaction of one pesticide with another. The types of pesticides to which our study participants are exposed include the organochlorines, organophosphates, carbamates, herbicides and defoliants, rodenticides, fungicides, and solvents and carrier substances.

To study the dose-effect relationship in humans, it is desirable to have people under surveillance who represent many gradations of exposure to a given pesticide. This, of course, is impractical in most instances. For the present we have settled for a comparative study of the minimally exposed general population and the chronically exposed people who work in the pesticide industries. These occupationally exposed people are not overtly ill. It is immediately apparent that we study the apparently healthy occupationally exposed workers, because if chronic exposure to a given pesticide chemical can cause effects in man, the effects are likely to become apparent most quickly, most frequently, most diversely, and most severely in the heavily exposed people. The heavily exposed volunteer study participants are selected from the ranks of pesticide workers; controls, matched by age, sex, race, and socioeconomic status, are selected from the general population. Selection of participants is based on history of exposure as well as chemical evidence of exposure. The study participants are given a comprehensive physical examination at least annually. At this time, a battery of biochemical, physiological, and behavioral tests are completed. Thereafter, at intervals varying from 2 weeks to 4 months, blood and urine samples from each participant are examined for biochemical changes and changes in levels of pesticides or metabolites. I must stress that we are not satisfied to look only for overt clinical illness in these people; we are looking for the much more subtle biochemical, functional, and behavioral changes which often are the earliest indication of organ damage. It is also important to understand that we are looking not only for the immediate or rapid change, which is often transitory, but also for the delayed and persistent change. It is our intention to continue this prospective surveillance of these study participants for at least 10 years.

A large number of people in a typical study community are occupationally exposed to pesticides and, therefore, are potential study participants. The major chemical industries may have plants in the area manufacturing the pesticide concentrates and technical grade chemicals. Occasionally their personnel are heavily exposed, usually as a result of an accident; but these people are well trained professionals working under alert and concerned management and are therefore safety conscious. Furthermore, the companies provide competent medical supervision of their staff. Thus, the pesticide worker in a modern manufacturing plant may not necessarily be exposed to significantly greater amounts of pesticides than the ordinary man on the street. Generally, driving to and from work may constitute a greater health hazard to this worker than does working with pesticides.

In contrast, many small formulating plants may operate in the study area, employing from 5 to 15 men. These workers, who generally are exposed throughout the entire year, prepare special formulations from the concentrates obtained from the manufacturers. One man may siphon pesticide concentrates into 5-gallon cans and dilute the material. Another man may bag toxic dust. These operations often are carried out in makeshift buildings without safety features such as adequate regulation of air movement. Often the operators have received minimal formal training. These people often work under the supervision of a nonprofessional man with a rudimentary knowledge of toxicology. Medical assistance is frequently available only when an accident occurs. We now have chemical evidence that many of these men are heavily exposed to pesticides. However, these men can effectively minimize their exposure by using masks and protective

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[2] Numerical references apply to the section REFERENCES CITED.

clothing. An important responsibility of community study project personnel is to encourage the use of protective devices.

The structural pest control operator is primarily concerned with treatment of buildings for termites, cockroaches, and rats. These men tend to specialize in one type of treatment and they often will have a favorite insecticide for a particular type of job. This is important to our project scientists because these men, in contrast to formulators, may be exposed to only one or relatively few pesticides. Characteristically, they have no fear of the compounds which they use regularly, and they could hardly be described as careful. They are sometimes heavily exposed, but they are able to stay on the job because they manage to avoid excessive exposure which results in overt illness.

In the southern tier of States, chinch bug and other plant infestations or diseases call for frequent lawn spraying. In some areas parathion and combinations of parathion and other pesticides are applied by lawn sprayers. These applicators use tank trucks equipped with hoses for spraying the toxicant directly on grass and shrubs. The proper and accepted method of application has been demonstrated to me. An operator, dressed in clean white coveralls, rubber boots, gloves, and mask, first makes certain the house is closed and toys are not in the yard. He informs the residents on either side of his client that he intends to spray, so children will be kept indoors. He then carefully sprays, reels in his hose, and departs; no spillage, no exposure. But I have also watched the same type of operation as an unannounced observer. As you can imagine, everything was different. No warnings to residents, no removal of lawn chairs or other objects, no concern that parathion was getting into a child's sandpile or inside the open windows of parked cars and buildings. Most importantly from the operator's standpoint, no masks, gloves, boots or long-sleeved coveralls were used. In this case, the clothes of the spray men were wet with perspiration, and stains on their trousers suggested possible dermal exposure with concentrated material.

Aerial applicator pilots, their ground crews, and operators of agricultural ground-spray equipment may be heavily exposed during the spray season. Pilots for the larger aerial applicator companies generally do not refill their spray tanks and, therefore, may not be excessively exposed. However, there are many one- or two-man operations or husband-wife spray companies. These pilots must load their own planes and may be heavily exposed. Even if the pilot does not load his own spray tanks, the man who does the loading is very likely to be heavily exposed. The flagman, who stands at the end of the sprayed field to indicate the swath, often has visible droplets of the spray mist on his glasses, suggesting that he may be receiving both respiratory and dermal exposure. While a flagman might be able to operate effectively with a degree of physical impairment resulting from exposure, a pilot's impairment might result in a fatal mistake.

Other people who are occupationally exposed include the supplier of fertilizer, since it is now common to mix pesticides with fertilizer; the farmer who applies seed germination inhibitors, herbicides, insecticides, and defoliants; people in the farm supply business who treat seeds with pesticides; mosquito-control men who dispense adulticidal fog or other insecticides; interstate and local drayage workers who transport large amounts of toxicants; firemen who fight fires in warehouses stocked with pesticides; farm workers who enter recently sprayed fields or orchards to cultivate or harvest crops. Surprisingly, the professional agricultural scientist may be heavily exposed because he keeps a small but potent selection of pesticides in his office or field car.

Results of previous studies of occupationally exposed workers (2, 3, 4) showed that in addition to causing acute toxicity, pesticides caused dermatitis and hay fever and aggravated certain allergies. Our studies comparing apparently healthy occupationally exposed workers and matched controls, while not yet completed, have provided some promising leads which are now being intensively studied. The proximal tubules of the kidney normally reabsorb more than 87% of filtered phosphorus; in chronically exposed men in at least one project, reduced reabsorption occurs more frequently than in controls (5, 6). Significant changes in the metabolism of certain amino acids have been reported (5, 6). Renal tubular reabsorption of filtered amino acids also appears to be reduced in the chronically exposed (7). In one group of chronically exposed men the renal excretion rate of phenosulfonphthalein was found to be significantly reduced (8). At one Community Study project glucose levels in blood of the chronically exposed workers were significantly higher than in controls (8). At another, the erythrocyte sedimentation rate was found to be inversely related to total pesticide usage (9). In another study, blood levels of the enzyme lactic acid dehydrogenase, similar in exposed and controls in the "off season," was significantly lower in the chronically exposed people during the spray season (9). Levels of serum alkaline phosphatase, an enzyme which the liver normally excretes in bile, have been found to be higher in the blood of apparently healthy workers occupationally exposed to the organochlorines (10). In cytological studies of sputum a much higher percentage of pesticide workers had squamous metaplasia and eosinophilia, compared with workers in other occupations (11). Significant cholinesterase depression without clinical illness has been detected in people occupationally exposed to the more toxic organophosphates (12, 13). Workers exposed to pentachlorophenol and heavy metals are reported to have greater frequency of sinusitis, bronchitis, and chronic cough (10). Dermatitis continues to constitute a frequent complaint of certain of the occupationally exposed (14). Porphyria has been noted in workers in plants where certain pesticides are made (15, 16).

Two other important means of gathering human-use experience with pesticides are studies of human volunteers and study of the poisoned patient. Although the Community Study projects do not have studies calling for the intentional exposure of people to pesticides, this remains the single most direct and efficacious way to obtain pesticide-use experience. Studies of human volunteers have several obvious advantages; the dose can be carefully controlled, and the subjects are under controlled conditions. The disadvantages, of course, are related to the possible dangers of such an experimental program. Any study involving man must be subjected to careful review by competent authorities prior to implementation, and human volunteers can be employed only when informed consent is obtained from them. The health and welfare of volunteers must be judiciously protected, in accordance with standards set forth by the Surgeon General of the Public Health Service (17) and by the American Medical Association (18).

The study of individual patients poisoned by pesticides can provide valuable information, not only on the chemical, physiological, and behavioral effects, but also on the dose-effect relationship, the ecological factors of importance, and the efficacy of presently available therapeutic methods. In agricultural areas poisoned patients are not uncommon. Reich et al. (19) have reported a study of pesticide morbidity and mortality in Dade County, Fla. During a 4-year period, from 1964 through 1967, there were 133 cases of documented pesticide poisoning in a population of about a million people. Attempted suicides accounted for 37 of the cases, accidents 61, and occupation poisoning 25. Eight cases were homicides and 2 were unclassified. Forty-seven of the 133 cases were fatal.

Nationwide, the death rate from poisonings caused by all solids, liquids, gases, and vapors was 5.0 per 100,000 in 1965.

The death rate associated with all pesticides in the United States was reported to be 1.0 per million population (20). We do not have reliable data on morbidity caused by pesticides, but Hayes estimated that for every fatal poisoning case there are 100 non-fatal cases (20). Thus, since people continue to be poisoned, the epidemiologist has an opportunity to assist the managing physician to determine the etiologic agent, the dose, the effects, contributing causes, and ways to prevent this public health problem.

Investigations of the acutely poisoned patient have resulted in our awareness of chemical or clinical effects worthy of further study. Holmes (12) reported definite but temporary deficiencies in memory, reaction time, visual and auditory responses, and muscular coordination during the first 3 days after organophosphate poisoning. The electroencephalogram may show definite changes (12, 21), and nerve conduction changes have been detected in the patient with acute toxicity (12). Studies of blood coagulation have indicated the occurrence, following acute organophosphate poisoning, of a phase of abnormally rapid coagulation, then a phase of prolonged coagulation (12). Glycosuria and proteinuria are common after acute exposure (12). Davies et al. (22) analyzed the clinical, chemical, and epidemiological aspects of 89 cases of acute organophosphate poisonings. The following disturbances were noted: depression of the enzyme cholinesterase, glycosuria, aminoaciduria, excretion of paranitrophenol, decreased phosphorus reabsorption, decreased ability to acidify urine, and impaired ability of the kidney to concentrate urine. These observations on poisoned people provide valuable leads for us to follow in the study of our chronically exposed long-term study participants.

Investigation of epidemics provides health officials with an understanding of the circumstances which led to the event, and provides a basis for planning preventive measures. The Tijuana epidemic investigated by Mexican officials (23) is a good example. More than 500 people reportedly became ill, and 16 were reported to have died as a result of parathion contamination of some ingredients of bread. A total of 874 people were hospitalized and 26 died in Arabia in 1967 when endrin leaked from drums stored above flour in the holds of 2 ships (24). In Texas, 23 farm workers became ill within 2 hours after they entered a cotton field sprayed the evening before with parathion (25). In a recent homicide 7 children died in Florida of parathion poisoning (26). Three men were made ill as a result of exposure to arsenine while repairing equipment in a pesticide plant in New Jersey (27). A father in Mississippi recognized his fly infestation problem, brought home a supply of a concentrated organophosphate insecticide, and proceeded to spray it liberally about the house. His infant, then his teen-aged son, then the father himself were successfully treated for severe organophosphate poisoning (28). Twenty newborn infants developed an unusual illness and 2 died in a small hospital as a result of exposure to sodium pentachlorophenate (29). These are but a few episodes selected to demonstrate the problem and the need for investigation of epidemics. Only when we understand the epidemiology of these poisoning episodes can we hope to prevent similar misuse of the chemicals.

While the pesticide industry has a good safety record in the United States, this is not necessarily true throughout the world. In Japan, Namba (30) reported more than 3,000 deaths from parathion alone during a 6-year period from 1953 through 1958. There is reason to believe that the safety record in many areas of the world is considerably worse (20).

Certainly, then, there are health hazards for man as a result of pesticide use. But put into proper perspective, the hazards which we presently recognize are related to improper storage and improper use of the chemicals, and man derives much more benefit from these chemicals than he does trauma. We are reminded again of the use and misuse of other valuable chemicals—barbiturates, ethyl alcohol, even aspirin. There is wisdom in addressing our efforts toward the proper use of these pesticide chemicals; prohibition, it seems to me, should be reserved only for unusually dangerous chemicals. However, we must continue to make objective studies, working in collaboration with industry, health departments, medical examiners, private physicians, and universities, to detect offending chemicals or degradation products and dangerous use patterns. This use experience with the heavily exposed people, together with responsible basic research, is our best means of protecting the public from deleterious effects caused by these valuable chemicals.

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THE PUBLIC HEALTH SERVICE PROGRAM IN PESTICIDES

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One cannot imagine an occasion more appropriate than your conference on "Pesticides, People and Problems" to discuss the Public Health Service's program in pesticides. Indeed, now when the lay and scientific communities are so greatly concerned about problems of environmental pollution and its potential impact on health, it is most necessary that the Public Health Service should mount and accelerate a program on pesticides, one of the major environmental stresses of our time.

The opportunity to tell you about this program is greatly appreciated. We would like to begin by making a few general observations about pesticides which we believe will serve to give needed emphasis to interrelationships between public health work at local and State levels and health efforts in the pesticides field in the Federal government.

Our generation of Americans has few problems more difficult or which press us with greater urgency than that brought into being by our long standing practice of dispersing poisons in our environment in enormous amounts and at an ever increasing rate now approximating 450 million pounds a year.

The difficulties of the environmental health problem posed by pesticides may be illustrated by the fact that we do not know very much, if anything, about the long-term health effects of a single pesticide chemical agent let alone the health impact of 200 chemical compounds which are regarded as of major importance as pesticides with respect to their volume of use and toxicity. What makes resolution of the pesticide problem urgent is the fact that pest control has become a part of our way of living.

Without pest control, modern agriculture would find it impossible to feed us not only abundantly but even adequately or to furnish us with timber and fibers. Without effective control of pests, moreover, we would be unable successfully to reduce the toll of insect-borne diseases which once plagued all mankind. Yet, for the great majority of control situations, effective methods which do not employ poisonous chemicals have not been developed.

Thus, we find ourselves in a most uncomfortable, perhaps even perilous, predicament. For until safer means have been found, we either must gamble with relatively unknown hazards inherent in massive dispersal of toxic agents or give up the demonstrated advantages of controlling forms of life hostile to our well-being and even existence.

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All of us would be delighted if it were possible at this time to be entirely reassuring about solutions to what quite properly has been called our great pesticides dilemma. But the best which can be said for the outlook now is that we are beginning to obtain the kind of cooperative government effort and the magnitude of resources which may prove equal to the task.

Through coordination of programs, many States are starting to attain more extensive employment of new approaches to pest control safety. Cooperation for the same purpose among State and Federal authorities is increasing.

For Federal agencies, an organization has been set up and procedures have been established for cooperative action on a regular basis. The recently chartered Federal Committee on Pest Control, successor to the Federal Pest Control Review Board, reviews and obtains modifications for the reduction of hazards in that five per cent of the nation's pest control activities represented by programs authorized by Congress. The Committee, established under the aegis of the White House, also coordinates pesticides monitoring efforts of various agencies and reviews for effectiveness and balance their pesticides and pest control research projects and information programs.

As a futher indication of the trend, agencies of the Department of Health, Education, and Welfare and the Department of the Interior may now participate with the Department of Agriculture in pesticide registrations which Agriculture only has the legal authority to issue and which every interstate manufacturer and distributor of the materials must have. This collaboration has been stipulated and implemented by written agreement of the Secretaries. Its objective, of course, is to obtain some reflection of public health and conservation viewpoints in Agriculture's pesticide registration decisions.

Undoubtedly keys to solutions of the pesticides problem will be provided primarily by scientific research. For this reason, we can be encouraged by the fact that resources for pesticides and pest control research of the Departments of Agriculture and Interior and of HEW agencies, including the Public Health Service, have been expanded greatly in the last few years. Of equal significance has been the marked increase in emphasis on finding satisfactory alternatives to chemical pest control.

These new efforts are producing some results. For instances, a special Agriculture research report more than a year and a half ago called attention to "outstanding control" of 20 serous insect pests through the use of biotic agents in the form of natural parasites or predators (1). There has been further progress along this line since this report was published. Meanwhile, somewhat comparable successes have been attributed to Interior Department investigations.

While such advances as these are heartening, it is necessary to point out that all sides frankly admit that non-chemical pest control agents, such as predators, or chemosterilants, or sex attractants cannot yet approach the effectiveness of chemical poisons and that their general use may be many years away. It also may be fairly observed that the Federal agencies sponsoring this research are limited in their responsibilities to efforts to safeguard and improve what may be termed the health of our agricultural and natural outdoor environments. While these agencies, to be sure, are concerned with the health of people, its protection is not their primary function. This is the basic responsibility, in the Federal government, of the Public Health Service (2, 3).

This has become a rather broad and significant responsiblity. To help make our efforts to discharge it more effective, the Office of Pesticides was established last November. It was placed directly under the Assistant Surgeon General in charge of the Service's Bureau of State Services (Environmental Health). The Office was given the basic objective of developing procedures for remedying, minimizing, or preventing adverse human health effects from environmental contamination by pesticides.

A major function of the Office of Pesticides is the extensive study of the toxicology of pesticides in experimental animals and man. Correlated with this basic research are important epidemiological studies on association of pesticide exposure to chronic disease. This will be alluded to later in more detail.

Pesticides research must be concerned with the varying poison capabilities of nearly 900 compounds, including the approximately 200 pesticides of primary importance. To this entanglement of variables may be added the circumstance that any one of the compounds may be incorporated in one or more of some 60,000 Department of Agriculture registered formulations none of which is likely to be toxic in precisely the same manner or degree to man, animals or plants.

New compounds and formulations, moreover, are being introduced each year and the whole mass of variants is further complicated by such factors as changing methods of pesticide application and widely differing farming practices, soil conditions, topography, water runoff characteristics, and weather among the thousands of communities where pesticides are used. Topping all this off is that fact that, while a good deal has been learned about acute poisoning from pesticides, little is known about their potential subtle long-term health effects. In general, appropriate retrospective and prospective epidemiological studies have not been conducted to determine if a relationship exists between environmental exposure and chronic disease.

As you may now fully realize, the Office of Pesticides has turned to communities in nine States, including your neighboring State of Washington, in joint efforts to obtain important information on the possible impact of pesticides in terms of disease induction. State and county health departments and academic institutions in the nine jurisdictions have direct responsibility to conduct, under our auspices, the first large-scale scientific investigations ever made to determine whether pesticides may cause long-term health effects in people under conditions of occupational or general environmental exposure. The research, as you also probably know, is expected to be extended to some other areas to obtain a composite of community experience which may be projected for the nation as a whole.

Five years or more will be required for the studies. During the research period, investigators will make extensive analyses of surgical biopsy specimens or post mortem samples of human tissues or organs, including liver, kidney, gonads, brain, and adipose tissue, to see if relationships may be found between pathological and physiological abnormalities and the pesticide levels in various environmental media. Particular attention will be given to the pattern of disease incidence among persons occupationally exposed to pesticides. In one State, available records permit study of the health experience of pesticide applicators as far back as 1948.

The community studies are expected to help fill many gaps now existing in knowledge of human health effects of pesticides. Much of the present information is inadequate in that it is related to short-term human investigations, or animal toxicity tests, or to acute cases of poisoning resulting from heavy accidental exposures. These have limited relevance to long-term exposure effects, especially those which may result from minute amounts of pesticides which have been encountered by the general population in this country for years.

These studies are to be supplemented by investigations, within or outside the research communities, of workers heavily exposed during the manufacture or formulation of pesticides or in pest control operations. These pesticide workers will be under surveillance for illnesses or abnormalities which may be related to exposure with the view to identifying high-risk individuals and groups for long-term epidemiological study.

We are hopeful that in a relatively few years the broad ecological epidemiological surgical studies of the community research projects in ten to twenty states will reveal some significant findings about the influence on people's health of repeated massive or continuous minute environmental exposures to pesticides. Supportive to such a wide-scale human population study is the very essential role of an intramural research and development capability in our own laboratories. You will be probably interested to know that we recently made arrangements to establish a

Pesticides Research Laboratory at Richmond, Florida. This Public Health laboratory will be located in a renovated and modified building on the South Campus of the University of Miami some ten miles south and west of the university's main campus at Coral Gables.

Our scientists in this laboratory will be in close contact with significant fundamental pesticides research being conducted for us at the university. They also will find it easy, because of the laboratory's location, to keep in touch with particularly promising work being done in conjunction with the Florida community study of pesticides.

A responsibility of the laboratory, of course, will be to help us supervise the quality of the community research as well as studies we support in non-government laboratories. Our new facility also will provide essential technical backup for our recommendations on manufacturers' applications for pesticides registrations. But the main task of our laboratory will be the conduct of new scientific investigations.

One of the most obvious of pesticides research needs is to know more about chronic effects of pesticides over a long period of time or the life span of test animals. This we plan to do and we should like also to find ways for more accurately extrapolating experimental work with animals to human experience. Currently available toxicity data simply are inadequate for making sound judgments as to the safety of existing pesticides, not to mention new ones appearing annually.

Little now is known about the relative importance of various routes of pesticides intake by man. We plan to explore these. Also relatively little understood are the effects pesticides and their metabolites may have on man either in combination with themselves or with other environmental chemicals man may ingest or absorb. We intend to investigate synergistic and antagonistic phenomena.

We believe there is a great need to know more about subtle effects of the micro insults of pesticides as distinguished from gross manifestations of toxicity. We expect to do some basic work on methods for determining impacts of pesticides on individual cells in terms of possible delayed inductions of physiological-pathological changes which may associate with the onset of illness.

The State of the art insofar as physicochemical methods of pesticide analysis are concerned, as you know, has progressed rapidly in recent years. Modern instrumentation and methods now permit us to measure concentrations of pesticides at the molecular level, in some media at parts per trillion. The quantification and, indeed, the identification of the wide spectrum of pesticides have transformed drastically our previous concepts on tolerances of pesticides, their absence or presence in the biota and at remote geographical areas. We who are

concerned about learning more about pesticides and health must be able to keep pace with these research advances by devoting attention to newer methods, to quality control in analyses, and to uniform reporting of analytical data.

As public health people you will recognize that one of the most important functions we can perform--and it also has meaning for researchers--is evaluation and surveillance of the extent and significance of the contamination of man and the environment by pesticides and their metabolites. Some of this work is involved in the community studies which will provide data continuously on the kinds and quantities of pesticides used and on their levels in people and in air, water, and other environmental media. Surveillance also is to be provided in epidemiological studies of population groups nationally selected for low as well as high exposure stress to get a wide range of experience. We will need and anticipate effective collaboration with other government agencies to make this work sufficiently broad in scope.

The Public Health Service and other agencies represented on the Federal Committee on Pest Control have been working to design systems for continuously monitoring pesticide levels, on a national basis, in air, water, soil, diet, and fish and wildlife. Meanwhile, the Office of Pesticides has begun to set up a National Pesticides Intelligence System. It is intended that this eventually will collect, collate, interpret, and periodically publish environmental pesticide exposure data. It is planned also that the system will collect and disseminate data and information pertinent to the pharmacology and toxicity of pesticides.

The clear purpose of the intelligence system is to provide guide-lines and criteria for the early recognition of hazardous accumulations of pesticides. It is probably unnecessary to call attention to the value of such a service for persons anywhere in the country who have responsibilities for public health protection.

Our discussion thus far has been concerned largely with the program of the Office of Pesticides solely because it is a new Public Health Service organization. There are, of course, established pesticide activities in other Public Health Service bureaus or research groups. These, although more familiar to you, are significant parts of what may be regarded as the total Public Health Service program in pesticides.

For more than 20 years, as many of you realize, pesticides have been under investigation in facilities of the Communicable Disease Center, a principal research organization of the PHS Bureau of State Services (Community Health). Members of the Center staff have become internationally recognized authorities on many aspects of pesticide toxicity. Moreover, they have effectively communicated--and are continuing so to communicate--results of distinguished research in scientific papers and articles and in frequent consultations with State and local health people, physicians, and others.

Elsewhere in the field of research, the National Institutes of Health, through some of the member institutes interested in categorical disease projects, supports pesticide research in areas of epidemiology, ecology, biochemistry, cytology, pathology and other disciplines through grants and contracts at universities and research institutes. There projects are related to such program interests as mental health, neurological disease, food protection and toxicology, allergy and infectious diseases, and cancer. The National Cancer Institute, for example, is financing several grant projects and some large contract projects to elucidate if possible the association of pesticide exposure to neoplastic disease and mechanism of action of pesticides in induction of cancer. Some pesticide chemicals have been demonstrated to be carcinogenic to experimental animals. Some investigators have implicated arsenicals in connection with certain human carcinomas. The current interest at the National Cancer Institute is in evaluating (a) the carcinogenesis of pesticide adjurants or synergists such as piperonyl butoxide and (b) the screening and bioassay of selected pesticides and their metabolites which have potential tumorigenic properties.

The Division of Water Supply and Pollution Control in the Bureau of State Services (Environmental Health) began full-scale investigation of water contamination by pesticides in 1959 and now is determining pesticide levels in water at about 130 monitoring stations on the country's major river basins. Clearly, this work is going to help us greatly in discharging our pesticides intelligence responsibility. Meanwhile, the division investigates the pressing question of pesticide runoff, seeks to discover the mechanism by which pesticides move through the aquatic food chain into fish and shellfish where concentrations reach toxic levels, and performs other needed research. Studies on the mechanism of massive fish kills in the lower Mississippi River basin are illustrative of the fine work of this division.

Some of the most significant work done anywhere on identification of and methods for safeguarding against pesticide contamination of milk and food has been accomplished by the Division of Environment Engineering and Food Protection, another Bureau of State Services agency. As you may know, the division's interest in consumer protection has resulted in development of model ordinances and codes covering pesticides in milk and food which many communities and States have adopted

In two other divisions of the Bureau of State Services some limited investigations have been underway. For example, the Division of Air Pollution has made some studies on atmospheric pollution in localities where pesticides are heavily dispersed. The Division of Occupational Health has supported, through contracts, studies of the epidemiological aspects of pesticide exposure under various occupational conditions in selected communities.

Certainly many of the state and federal agencies are currently engaged in the various facets of the pesticide dilemma whether it be conservation of fish and wildlife, concern for human health, the search for remedial measures or development of alternate procedures for pest control. The tempo of the national program is increasing in diversity of effort, budgetary support, and volume of published literature. Resources in facilities and manpower are being rapidly developed to meet objectives.

In summation of the public health problem it may be appropriate to draw attention to certain parameters not usually considered or perhaps overlooked...previous biological assessments of pesticide exposure. Acute massive exposure to pesticides with concomitant poisoning has been adequately emphasized in humans but little attention has been given, if any, to subthreshold response of pesticides. The induction period of some chronic diseases, especially cancer, may be of the order of 15 to 20 years particularly where the cellular insult is of low concentration or dose. Interestingly enough, this observed induction period is in the same time range as the national experience in the general use of synthetic organic pesticides.

In the overall evaluation, therefore, of this environmental stress, one must consider and resolve the effect of repeated episodes of poisoning, the cummulative action of which may influence man's performance or recuperative powers. Furthermore, with the constant exposure to pesticides in the body organ, tissues and environment, there is the distinct possibility that there may be a threshold for metabolism of pesticides in a system now flooded with other exogenous or endogenous agents all of which are capable of inducing disease. Finally there are those individuals in the general population who are so genetically constituted that they may react differently or respond fatally to the environmental or the occupational challenge of a pesticide. Such individuals who lack an important enzyme system to metabolize the chemical or who, because of liver impairment, cannot detoxify the chemical pesticides, present interesting population groups for study and classification for ultimate preventive or control procedures (4).

It seems quite clear today that we are far better equipped at local, State, and Federal levels to cope with the pesticides problem than we ever have been. It also appears that our capabilities in this field will increase. But it also is quite evident that we are going to have to reconcile ourselves to many years of hard work before we attain our objective of knowing all that we need to know about the health effects of environmental contamination by pesticides and how most effectively to deal with them.

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Some Health-Related Needs in Pesticide Investigations

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PESTICIDES PROGRAM
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The universal presence of pesticides in man, from the fetal stage on, calls for many studies: evaluation of toxicity in the fetus with reference to prematurity, pre-eclampsia, birth defects, etc., studies on detection of metabolites; disposal of pesticide wastes; chemical epidemiology; monitoring of occupationally exposed people; training programs for analytical chemists; many others.

It is entirely fitting that the Sixth Inter-American Conference on Toxicology and Occupational Medicine has selected pesticides as the topic for discussion. Diseases caused by non-viable entities in our environment are belatedly getting some of the attention that they have long deserved, and pesticides are an important part of these media. Pesticides confront us in ever increasing numbers and formulations, and they are not going away. They are in the food we eat, the air we breathe, and the homes we live in. Each of us carries his own body burden of pesticides. They are inescapable, and it behooves us to study them, to understand them, and to use them safely. This does not imply that pesticides are doing us harm; it does constitute a clear command for us to find out exactly what risks are involved in their use. Considerable progress has already been made in this area; however, instead of relating progress, of which you are aware, I propose to cite some needs which I hope will be a challenge and an inducement to intensify efforts for the safer use of a very valuable armament to our survival.

First of all, evaluation of the toxicity of new pesticide chemicals involves a considerable portion of the effort of most toxicology laboratories. The need for this work is obvious, and closely related to it is the problem of screening test pesticides for toxicity to man. Data from animals can only be a guide, and there is often a great difference between toxicological effects on different animals. Better test animals are needed, and where safe and feasible, there is no substitute for human volunteer studies.

We know that there is a problem of potentiation or antagonism in the simultaneous exposure to certain pesticides and certain drugs, as well as between some pesticides. The extent of this is a moot question. The toxicity of a pesticide from its use alone does not necessarily indicate its potential toxicity when used in combination with other chemicals, and this problem needs further investigation. Dr. Deichmann, the Director of this Conference, has contributed substantially in this field.

It is known that the fetus in utero is storing organochlorines, at least as early as the fourth week of gestation. The effects of the low levels that now occur may be of no consequence to an adult, but a study should be made of the effects of these compounds on the fetus with particular reference to prematurity, pre-eclampsia and eclampsia, abruptio placentae, stillbirth, birth defects, spontaneous abortion, and congenital or infant malignancy.

The analytical problems in dealing with pesticides are legion, and a great deal of work is needed on the quantitative detection of more compounds in more types of substrata. The development of analytical procedures for detection of metabolites of pesticidal compounds is necessary before their metabolism and site of action in the animal body can be understood. The data reported from various laboratories are often difficult to correlate because of differences in analytical procedures. Rigid standardization is detrimental to progress, but data comparisons would be more meaningful if some standardization could be adopted by the various laboratories, at least until clearly better methods are devised.

There has been a relative lack of epidemiological investigations of chemical poisonings. Most epidemiologists have a background in infectious diseases, and few have been concerned with chemical epidemiology. More attention should be given to the prevalence and distribution of toxic chemicals in man and the environment. Concurrently, the determination of the prevalence and distribution of clinical and subclinical pathology in man is needed to discover and evaluate any causal or contributory relationship to pesticides.

Most State health departments have not given or have only begun to give attention to the many problems of recent origin resulting from our chemical environment. All State departments of health should be developing a surveillance system which could be used for monitoring occupationally exposed people. The appropriate routine analysis of blood and urine of heavily exposed workers, regardless of the chemicals to which they are exposed, would, in most instances, give warning of potential danger. This does not preclude the establishment and use of proper threshold limit values in air. The need for every area to have available an experienced forensic pathologist and a competent toxicological service is only too evident. More training programs are needed so that all State and many local health departments may have on their staff a trained analytical chemist and an epidemiologist well versed in the investigation of chemical poisoning. I might say that the Pesticides Program of the Public Health Service is anxious to help in this endeavor.

As a corollary to epidemiological and surveillance activities, routine monitoring of man and the environment is essential. Monitoring programs are being carried out by several government departments, and a monitoring journal which carries information on pesticide levels wherever they may exist, is now being published by the Pesticides Program for the Federal Committee on Pest Control. Several years of such work with more standardized analytical procedures should provide a better basis for epidemiological extrapolations.

There are probably 100,000 cases of poisoning from pesticides in this country each year, with some 150 accidental deaths. Yet, poisoning has not been declared a reportable disease, while at the same time, many far less important diseases are required to be reported. We need to know from a clinical and epidemiological point of view who gets poisoned with what, and where, when, how, and why. Until we can see the entire iceberg, it is hard to evaluate its magnitude.

Information that can prevent pesticide poisonings is available, but it must reach the public before it can accomplish its purpose. There is a great need for public information on pesticides, particularly at the local level. Many of the poisoning cases reported to us, all too clearly could have been prevented if public information had been adequate.

Better diagnostic procedures are needed, since pesticide poisoning may mimic many other conditions, and oftentimes a diagnosis is based on association rather than clinical signs and symptoms. Improved analytical, biochemical, and clinical tests are needed that can be adapted for routine use in small laboratories and even in the field.

The mode of action of many pesticides is not understood. A clearer understanding of this would be the starting point for the development of specific treatment. There is, at present, a great need for a specific antidote for cases of chlorinated hydrocarbon poisoning. Treatment is needed not only to counteract the symptoms, but to get to the site of action and reverse the effect. The problem is finding the mode of action. The importance of this is obvious.

A problem of increasing magnitude is the handling and disposal of pesticide wastes and used containers.

We have given this problem much consideration, and the Federal Committee on Pest Control has a special subcommittee appointed to study it. In spite of this, no practical solution has evolved. Waste disposal from manufacturing and formulating plants is handled in a variety of ways often resulting in contamination of the environment in the vicinity and pollution of streams for long distances.

In agricultural areas of heavy pesticide usage, the disposal of containers is a formidable problem. Abandoned pesticide containers are strewn throughout the entire length of the Mississippi levee. A system of returnable drums or of easily disposable containers and an organized plan of disposal is a *must*. Certain bacteria and fungi are apparently acclimated to metabolism of specific pesticides. Strains of bacteria have been developed that utilize DDT as a source of energy, converting it into CO_2 (Johnson, R. F., Personal Communication, February 1968). There may be other organisms that would break down toxic chemicals to harmless materials. Investigations are needed to determine if such methods can be used for the problem of pesticide waste disposal or for ridding areas of accumulated residuals.

A related problem involves the transportation of pesticides and their storage. I need only mention the recent incidents of large scale human poisoning in Saudi Arabia, Qatar, Tia Juana, Jamaica, and Colombia as an example of the importance of the problem. Fortunately, and surprisingly, it has not happened here. The U.S. Department of Transportation lays down regulations governing transportation of hazardous materials, and these must be familiar to and followed by all concerned if such incidents are to be prevented. One real problem is storage of pesticides with edible products after they reach their destination. This is a State and local matter which desperately needs attention.

We frequently get requests from States for help on fo.mulating legislation governing the control of pesticidal chemicals. There is a great need for more uniformity in State regulations governing the use, transportation, and storage of pesticides. Efforts are being made by the Public Health Service and the U.S. Department of Agriculture to assist the States in this regard. Fortunately, there is already a considerable uniformity regarding the registration of pesticides.

The transport mechanism of pesticides through the environment is inadequately understood, even that resulting from the runoff from farm land. The biological magnification of pesticides in their passage through the food chain needs to be further investigated. As an example, in one study of lake water treated with DDD there was a concentration in the water of 0.02 ppm immediately after treatment. Residue levels 13 months after treatment were 10 ppm in plankton; in fat from plankton-eating fish, 903 ppm; in fish from carnivorous fish, 2690 ppm; and in fat from fish-eating birds, 2134 ppm. This represents a 500-fold increase in levels in plankton and a 100,000-fold increase in fish-eating birds over levels occurring in lake water after treatment.[1] There is no indication that the intake of pesticides in man's food is of any significance healthwise, but man who is at the end of his food chain should find out.

Nearly a billion pounds of pesticides are produced in this country each year. We do not have sufficient knowledge of where these pesticides are being used. If we had accurate recording of the use patterns of pesticides, we might be able to correlate observed effects with pesticides used. We would also be able to anticipate problems which might be likely to develop in particular regions. The problem of recording the use pattern of pesticides is a difficult one and must be considered in relation to other pressing needs.

Presently, a considerable effort is being made to substitute other methods for chemical control of insects with the idea that they would be less hazardous to health. This matter was considered by the 16th Meeting of the World Health Organization Expert Committee on Insecticides in September 1966. They concluded that a biological agent or the toxic product of an organism will not necessarily present either a greater or lesser health hazard than a synthetic material. Contrary to the popular belief that "natural" substances are harmless, they pointed out that the most poisonous materials known are in fact, of natural origin. Finally, they concluded that any material, living or dead, that is proposed as a pest control agent should be submitted to the same searching examination for potential toxicity to man as is applied to synthetic pesticides. Particular attention was called to hazards that might be inherent in the use of fungi since some of these are incriminated in some of the most serious of human diseases. If and when other methods supplant the use of chemicals as pesticides, the toxicology problem will not be eliminated, but only changed.

These are a few of the many problems that confront us. Their solution is a challenge to our ability and a necessity to our well-being.

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Los pesticidas son elementos presentes en nuestro medio ambiente y es importante manipularlos con medidas de seguridad. Métodos para determinar el riesgo que los mismos representan para el hombre deben ser mejorados. La exposición simultánea a distintos pesticidas implica problemas de aumento de potencia y antagonismo. Es necesario conocer el almacenamiento de los insecticidas cuando el feto aún se encuentra in utero. Es necesario mejorar los métodos analíticos. Otras áreas que requieren estudios son la epidemiología, vigilancia de las personas expuestas en su trabajo, determinación de la concentración en el medio ambiente y que las autoridades sean informadas de los casos de intoxicaciones. También es necesario desarrollar métodos diagnósticos, así como modo de acción de los pesticidas. Es necesario que los estudios desarrollen programas de entrenamiento para químicos y epidemiologos, y hacer conocer al público cómo manipular estos agentes. Se sugiere uniformidad en las regulaciones estatales.

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The Pesticides Program Activities of the Public Health Service

SAMUEL W. SIMMONS, Ph.D.

PESTICIDES have made significant contributions toward elevating our standard of living during the 20th century. They have controlled malaria, typhus, dysentery and diarrhea, plague, and other diseases transmitted by insects. They have also brought vast economic and social benefits through better health and increased quantity and quality of foodstuffs, feed, and fiber products.

In less than 20 years, the use of synthetic chemical pesticides in the United States has increased from a level of a few million pounds a year to nearly 1 billion pounds annually. Almost 60,000 pesticide formulations are now registered in the United States, and each of these contains one or more of the approximately 800 different pesticide compounds.

The increased production and use of pesticides, accompanied by heightened public interest in contamination of the environment by these compounds, led to the establishment of a focal point within the Public Health Service for assessing the total impact of pesticides upon human health. This responsibility is assigned to the Pesticides Program of the National Communicable Disease Center.

For many years the Service has taken an active interest in the health aspects of pesticides. Early studies on the agricultural pesticide, lead arsenate, were carried out by scientists from the National Institutes of Health.

The National Communicable Disease Center began work on pesticides in 1949, with the establishment of a toxicology laboratory at Savannah, Ga. Since that time the activities of this laboratory have been focused on continuous research concerning the safety and effectiveness of pesticides for the control of vectorborne diseases. Early studies helped to demonstrate the safety of DDT and thus permit its use against vectors of diseases such as malaria, typhus, and plague. Research has also included medical study of farmers, aerial sprayers and ground applicators of pesticides, and employees of pesticide manufacturing plants whose work necessitated intense and prolonged exposure to pesticides. Similar studies have been made of volunteers who received known doses of important pesticides. Many cases of accidental and occupational poisoning have been investigated. The storage and excretion of pesticides and their metabolites have also been measured in the general population and in persons whose exposure to pesticides was exceptionally high.

The Office of Pesticides, established in Novem-

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At the time this report was prepared, the Food and Drug Administration was not a part of the Public Health Service; therefore, its work in the field of pesticides is not included.

ber 1964, provided a mechanism for responding to a number of health-related recommendations which followed a comprehensive study of the benefits and hazards of pesticides by the Life Sciences Panel of the President's Science Advisory Committee. In August 1966 the Office of Pesticides was transferred from its Washington, D.C., headquarters to its present site at the National Communicable Disease Center in Atlanta and consolidated with the toxicological activities of the Center. This new organization was named the Pesticides Program. (On July 1, 1968, the Pesticides Program was transferred to the Food and Drug Administration.)

The understanding of the ultimate impact of pesticides on human health requires the efforts of workers in many disciplines. In addition to research on the assessment of long term and short term effects of these compounds on people, the research personnel are aiming at corrective solutions to pesticide-health problems.

The work of the Pesticides Program is carried out in community studies; State programs, which include monitoring of air and people; and research laboratories. The sites of these activities are shown on the map.

Community Studies on Pesticides

The community studies on pesticides consist of epidemiologic and ecological studies in selected areas of heavy pesticide usage throughout the United States and Puerto Rico. Sixteen of these studies, which are carried out under contract with State and local health departments and universities, are now underway. Within each study area a pesticide-usage profile is developed. Data are obtained continuously on the types and quantities of pesticides used; the time, location, and method of application; and the purpose for which they are used. Concurrently, levels of pesticides and their metabolites in people and environmental media are determined. These data should eventually provide information on the movement of pesticides in the environment and their routes of entry into man, the importance of potential sources of contamination for man, as well as clues to the metabolic fate, excretion, and deposition of pesticides.

Investigators assigned to these projects study people who receive heavy exposure to pesticides; for example, workers in pesticide formulating plants, pest control operators, greenhouse workers, and aerial spray pilots. Study procedures for each participant generally include a detailed history of pesticide exposure and usage, a complete medical history and physical examination, and hematological and biochemical tests. Pesticide residue analyses are performed on urine and blood and, when samples are available, on adipose and other tissues. Through this complete spectrum of studies of various population groups, information is sought on the potential effects of exposure and use in terms of disease induction.

Community studies have led to development of laboratory competence in pesticide analysis and allied tests, and each community laboratory performs all testing for its own area. All laboratories participate in a quality control program that is designed to insure a satisfactory standard of technical performance. Concurrently, the Pesticides Program provides technical support, which includes repository services for reference pesticides, analytical quality control, methodology research, and training in analytical methodology.

Generally, community studies are undertaken in areas where pesticides are applied frequently and in large amounts. Because of the wide variation in climates, growing seasons, and agricultural practices in these areas, the long term effects of pesticides can be studied under varying conditions.

The Texas study is in the agricultural area in the southern tip of the State where warm temperatures and modern irrigation practices permit an unusually long growing season. Massive amounts of insecticides, herbicides, and defoliants are applied by aerial sprayers and ground applicators. Numerous persons are occupationally exposed, and acute illnesses frequently occur as a result of accidental exposure. These illnesses are investigated by the study personnel. Exposed persons are kept under biochemical, medical, and physiological surveillance and hospitalized when necessary.

The characteristics of the site of the Idaho study differ greatly from the Texas site. In this area pesticides are applied in large amounts during a comparatively short growing season. Research also includes close surveillance of ex-

Pesticides Program activities of the Public Health Service

posed persons, especially those who reside near heavily treated areas.

The New Jersey community study is in a highly industrialized area. Here, intensive surveillance is maintained of persons involved in the manufacture and formulation of pesticides. The South Carolina study also closely follows the employees of formulating and manufacturing plants, in addition to the study of farm families and persons involved in the application of pesticides.

The Florida study is continuing a statewide program designed to maintain liaison with all structural pest control operators, even after they have left the industry, to determine their health status over a period of years. In the Dade County area, where large amounts of organic phosphorus insecticides are used extensively, a number of pesticide poisonings occur. The Florida project studies biochemical and physiological changes in poisoned persons and is also concerned with improving patient management and therapy.

The Iowa community study is seeking a possible causal relationship between pesticide exposure and prolonged recovery time of pesticide-exposed surgical patients who have received the muscle relaxant, succinylcholine. Other studies underway deal with man's exposure to pesticides through his food chain—investigating levels of pesticides in people as related to pesticides and their metabolites present in locally grown livestock and other foods.

In addition to the studies of occupationally exposed workers, the Mississippi study maintains close surveillance on pilots of pesticide spray planes, since 26 percent of all U.S. fatal crashes of spray planes in 1964–66 occurred in the area of the Mississippi River Delta. All community study projects investigate crashes of pesticide spray planes. The investigations are carried out under an agreement with the Bureau of Aviation Safety and the Federal Aviation Administration of the Department of Transportation.

The Michigan and Washington State community studies are in the center of fruitgrowing regions. These studies are concerned with

the effect of spraying operations on orchardists and people living adjacent to fruit orchards. Also, the Washington project is re-examining approximately 1,000 persons who had prolonged occupational exposure to lead arsenate and were originally studied in 1938 by Dr. Paul Neal of the National Institutes of Health.

The Louisiana study is concerned with agricultural workers and family units in southeastern Louisiana and pest control operators in New Orleans. All community studies include long term surveillance of population segments receiving heavy exposure to pesticides. Also, each study acquires ecological data on the movement of pesticides in the environment of its area.

The Puerto Rico project is determining the types and amounts of pesticides used there, characterizing the populations heavily exposed to pesticides, and considering the morbidity and mortality data in view of pesticide use patterns.

The Hawaii community study, in Oahu, is conducting an islandwide survey of the possible relationship between maximal daily household use of pesticides and certain chronic respiratory diseases. In addition, a study is presently being conducted on the relationship of pesticides to cardiovascular disease, asthma, bronchitis, and sinusitis. This is carried out in cooperation with the National Institutes of Health Hawaiian cardiovascular study and the Hawaii Department of Health.

The Utah study, at Salt Lake City, provides regular medical and biochemical surveillance of occupationally exposed workers who apply pesticides to the extensive marshy lake beds characteristic of the Great Salt Lake Basin area. It also proposes to analyze water, fish, and muck in watershed areas.

In Weld County, Colo., location of the Colorado community study, a multiple regression study is being made to determine the source of families' exposure to pesticides. Potential sources—house dust, soil, food, water, and drift from treated fields—are evaluated. These family units are under continuous medical and biochemical surveillance.

The Arizona community study is comparing pesticide exposure levels, pesticide concentrations in blood, and clinical characteristics (physical and biological) in five urban and five rural families. The rural families reside in an area which is sprayed intensely in the summer months. Close surveillance is also maintained on aerial spray pilots and loaders for total DDT levels in blood as well as cholinesterase levels. Current knowledge indicates that these workers, particularly loaders, receive the highest exposure to DDT and the cholinesterase-inhibiting compounds.

In California, studies include blood dyscrasias in a sample of the population regularly exposed to lindane and the possible causal relationship between seasonal neonatal jaundice in the Imperial Valley and the use of cotton defoliants.

The data gathered from the various community study projects will eventually form the basis for a clearer understanding of the benefit versus risk equation of pesticides as related to human health.

State Services Program

A major goal of the Pesticides Program is to help the States improve their technical capabilities in dealing with the public health aspects of pesticides. Assistance and guidance are currently being given through various training and consultation activities, ranging from formal courses in analytical techniques to consultation on legal aspects of pesticide application and use. In addition to training courses on the chemistry and measurement of pesticide residues, organized courses and on-the-job training are offered in the epidemiology, diagnosis, and treatment of pesticide poisoning. Also, persons who perform or supervise pest control operations are instructed in the health hazards of pesticides encountered in their particular work.

Courses are conducted in Atlanta, Ga.; Perrine, Fla.; and Wenatchee, Wash., where laboratory staff members and equipment are used as integral components in the training program. Courses are also given in cooperation with State and local health departments. The first course of this kind was given recently in conjunction with the New York City Department of Health, and others are scheduled. More than 350 physicians, scientists, administrators, educators, and businessmen who have varying interests in pesticides and health attended these courses in 1967.

In tandem with the various courses offered,

films, slides, educational exhibits concerning health aspects of pesticides, and various types of printed information material are available to interested groups. A new film entitled "Perspective on Pesticides" is available to each State health department.

Legal consultation is offered to States, upon request, concerning specific problems of legislation, enforcement, and uniform regulations with respect to pesticides. Evaluation of State pesticide laws, recommendations for more complete and efficient State and Federal statutes, and continuing legal guidance to the Pesticides Program staff are among the activities undertaken by the State Services program.

Another function of the State Services program is systematic monitoring of pesticide levels in a broad sample of the general U.S. population. People are being monitored by the analysis of tissues collected from post mortem examinations and from tissues excised in the normal course of surgery. Limited clinical data are obtained for each specimen. Tissues are being collected at more than 70 selected hospitals throughout the United States and sent to contract laboratories for analytical testing. To assure comparability of results, procedures are standardized for the collection and handling of tissues, analytical methods and equipment used, and the reporting of information. Because of limitations in the availability of practical analytical procedures, sampling is limited to adipose tissue and blood serum, and testing at this time is restricted to chlorinated hydrocarbon residues. However, as procedures are developed and evaluated, additional tissues may be used and testing will be conducted for other compounds.

Air across the country is being monitored to provide information about the extent and severity of pesticide contamination of the atmosphere in order to evaluate the importance to man of this route of exposure to pesticides. The areas selected for air sampling represent different conditions of pesticide use as well as climatic variations. Determinations are made of pesticides present both as vapors and particulates, and meteorological factors and diurnal variations are also studied. Data from this study will subsequently be used to evaluate the need to monitor pesticides in air in other selected key areas throughout the country. Efforts are also being directed toward the development of a mobile automatic air sampler-analyzer.

Another aspect of the State Services program is the collection, storage, and dissemination of information and data related to the health aspects of pesticides. The two principal types of information are research data from all sections of the Pesticides Program and references to published work. The references include, as far as possible, worldwide publications relating to the health aspects of pesticides. Data from the research laboratories, the monitoring of people and air, and the community studies are statistically analyzed, coded, and stored by computers for retrieval. Statisticians in the State Services program assist other sections of the Pesticides Program in solving problems of statistical design and analysis of data.

The State pesticides projects are a new function of the State Services program. Their purpose is to determine pesticide-related health problems within the States and to improve State and local competency in handling these problems. Each project consists of a multifaceted program including training in the safe use of pesticides, surveys to develop pesticide usage profiles, pesticide legislation review, environmental (air) monitoring, monitoring of people, morbidity and mortality reporting, and comprehensive planning and activating of programs on the public health aspects of pesticides. The projects are being conducted by a Public Health Service employee assigned to a State or under contracts whereby a State employs someone to conduct the program. Presently, project leaders are on duty in Connecticut, Illinois, Kentucky, Ohio, Oklahoma, Oregon, and South Dakota. Negotiations are also underway with other States; plans call for the development of 13 of these projects.

Research Laboratories

Toxicology Laboratory. The Atlanta-based Toxicology Laboratory is the primary center within the Public Health Service for studying effects of pesticides on human health and for developing and testing improved methods to diagnose and treat pesticide poisoning in man. The research program is aimed principally at the development of new data on acute and

chronic toxicity of economic poisons. This laboratory also conducts studies of people who suffer heavy environmental exposure to pesticides and of volunteers who are experimentally exposed in order to determine toxic influences on their health status and to measure total body burdens of pesticides and their metabolites. Improved diagnosis and treatment of pesticide poisoning are sought through tests with experimental animals, from studies of poisoning cases, and by research on the mode of action of compounds.

The Atlanta laboratory gives emphasis to studies on man. Two such studies have included daily feeding of known doses of DDT to volunteers. The doses given ranged up to 200 times the level being ingested by the general population as a residue in its daily diet. Feeding of this amount of DDT for periods up to 21 months did not produce detectable harmful effects, as indicated by periodic physical examinations throughout the dosage period and by clinical and laboratory tests. During these studies, a method was devised to measure DDT absorption which included urinary excretion of the DDT metabolite, DDA.

These earlier studies on volunteers increased the value of a more recent study of 35 men who had formulated DDT for 11 to 19 years, because they provided information on the relationship between dosage on one hand and storage and excretion on the other. The average absorption of the compound by 20 of the men judged to have received heavy occupational exposure was more than 400 times greater than the current absorption by the general population.

Continuing studies with experimental animals are concerned with determination of the acute and long term dermal and oral toxicity of compounds presently in use or proposed for use as pesticides. In one study, monkeys were fed various levels of DDT in their diet for more than 7 years and studied to determine effects.

Pesticides Research Laboratory, (Western). The Western laboratory is located in Wenatchee, Wash. Scientists at this laboratory study health hazards associated with the use of pesticides. The intensive use of pesticides in the fruit orchards of this area and the fact that many residents have their homes adjacent to orchards provide ample opportunity for field study of both occupational and environmental exposure to a number of pesticides.

Emphasis at the Western laboratory is given to the measuring of exposure to pesticides of manufacturing personnel, formulators, applicators, and other environmentally exposed population groups; to measuring absorption of compounds under use and exposure conditions; and to correlation of exposure data with physiological and clinical effects in the persons exposed. Studies are also made of cases of pesticide poisoning which occur in the Western States. The laboratory provides technical assistance to community study projects and to State and local health departments in the Western States.

Investigators at the Western laboratory have made a number of significant contributions to the knowledge of health hazards in the use of pesticides. One multifaceted study included determination of general contamination of the environment with DDT. The storage level of this compound in body fat of the general population was determined to be about 4 ppm, with a range from 0.7–25.4 ppm. Levels in persons receiving environmental exposure were found to be not significantly higher than those in the general population. However, levels in persons receiving occupational exposure increased in direct correlation to the intensity of exposure. Analysis of complete meals indicated that the general population ingests about 0.04 mg. of DDT per day in food. Calculations indicate that this amount is sufficient to account for most or all of the storage level detected. The DDT content of women's breast milk was found to be about 0.1 ppm in whole milk or about 2 ppm in the fat moiety.

Investigators at the laboratory have also developed methods for measurement of dermal and respiratory exposure of workers to pesticides. These methods have been applied to approximately 10 pesticides under 31 different conditions of use. Studies are made of protective clothing and masks which might reduce exposure of workers. Before its general adoption as an approved drug, 2-PAM, the antidote for poisoning by organic phosphorus compounds, was made available to physicians and hospitals in the Northwest. Some 50 poisoning patients have been treated with this drug. The favorable results of this treatment provided

valuable support for the ultimate acceptance of the antidote as an approved prescription drug.

Pesticides Research Laboratory (Florida). The Pesticides Research Laboratory at Perrine, Fla., is the primary reference, quality control, and methodology research facility for all sampling and analytical methods used by the Pesticides Program. This laboratory also is a major center for training personnel in pesticides analytical methodology; its staff is responsible for keeping pace with advances in analytical techniques. The rapid advancement of pesticide analytical chemistry in recent years has brought major improvements in the sensitivity of instruments and methodology. The introduction of gas chromatography in particular, and the availability of various selective types of detectors, now make it possible to determine microconcentrations of pesticides in the parts per billion range and, in some instances, in parts per trillion.

A prime effort of the staff is to make new and improved reliable analytical procedures available to the laboratories of the community study projects and those of State and local health agencies which assess pesticide residues in people and the environment.

The laboratory is also concerned with research on the fate and metabolism of pesticides in animals in order to determine their physiological, anatomical, and genetic effects. The data collected will be used as an index to new knowledge of the impact of pesticides on the health of man. This laboratory conducts studies on the acute and chronic toxicity of pesticides to mammals, with emphasis on studies of chronic effects. Research includes studies on biochemical and other pesticide-induced changes which may directly or indirectly lead to diseases in man. Special investigations are underway using squirrel monkeys and rhesus monkeys.

Registration of Pesticides

Federal law requires that all pesticides be registered with the U.S. Department of Agriculture before they can be sold in interstate commerce. The Pesticides Program reviews pesticide registration applications with respect to the human health hazards which may result directly or indirectly from the proposed uses of these compounds.

Under a three-way agreement by the Departments of Agriculture, Interior, and Health, Education, and Welfare, the staff of the Pesticides Registration Section in Washington, D.C., reviews the applications from the standpoint of possible hazards to human health that would result if the registration were granted. Particular attention is given to the accuracy in labeling and cautionary statements; directions for use, dosage, formulation, and mode of application; persistence of the compounds; purpose of proposed use; hazards to applicators and the public during and after the application; and the degree of environmental contamination that may result from the proposed use. In the review process, emphasis is placed on evaluating the acute and chronic toxicity data on all active pesticide ingredients including skin absorption, inhalation, potentiation, and synergistic properties. An average of 300 applications are received weekly. Other technical personnel within the Pesticides Program provide valuable supportive data on the toxicity of pesticides and on the levels of these compounds in man and the environment.

Conclusion

The Pesticides Program of the Public Health Service is concerned with the assessment of the total effects of pesticides on the health of man in order to deal effectively with health problems associated with the use of pesticides. This mission requires the efforts of many trained persons, in various disciplines, in order to provide the basic laboratory research, epidemiologic and ecological studies, as well as consultation, training, and information services needed to evaluate more completely the risks entailed in the use of pesticides against the background of their great benefits.

PESTICIDES PROGRAM ACTIVITIES

JUNE – 1968